

**NEUROPSYCHOLOGICAL OUTCOME
FOLLOWING NEUROSURGERY FOR MENTAL
DISORDER.**

ALISON A. LIVINGSTONE

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DECLARATION

“This thesis has been composed by myself and I certify that it is a true and accurate account of the work carried out.”

Signed ...

Alison A. Livingstone

ABSTRACT

Neurosurgery for mental disorder (NMD) continues to exist as one of a range of treatments available to individuals who experience severe and intractable psychiatric illness. Historically, this particular use of ablative neurosurgery has attracted a considerable amount of interest and controversy. Despite modern advances in both technical procedure and understanding of the disorders for which NMD is indicated, the irreversibility of these procedures continues to attract attention from both public and professional groups alike. To date, indisputable evidence regarding the efficacy and frequency of adverse effects has not been established. Therefore, the primary aim of the present study was to investigate the neuropsychological outcome following neurosurgery for mental disorder. In light of previous research, the specific aims were designed to elucidate the impact of such procedures on aspects of both general and executive functioning, through means of clinical and computerised neuropsychological assessments. As such, pre- and post-operative performance scores of an entire population of surgical candidates at a national centre for the provision of NMD were examined. The principle investigation focussed on a group of 22 individuals of mixed diagnostic categories, all of whom had undergone treatment by anterior capsulotomy. Within-subjects comparisons revealed the overall stability of post-operative performance as measured by tests of general cognitive and executive function, at follow-up periods of two weeks, one year, and in a sub-group of individuals, two and a half years post-operatively. A small number of statistically significant improvements and impairments were noted, and along with the general trend of improvement observed at long term follow-up, are discussed in the light of related research.

CHAPTER 1 – INTRODUCTION

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1.1 NMD – Background Information

1.1.1 Introduction

The forthcoming introduction to the field of neurosurgery in the treatment of mental disorder has emanated from an investigation of available scientific literature, both past and present. Initial exploration of background information was gathered through use of *Psychological Abstracts*. Subsequently, the majority of key references were obtained through ongoing literature searches utilising the following key databases, *PsychInfo*, *Medline*, *EMBASE* and *The Cochrane Library*. Such examination of the literature revealed that the evidence base within this field of research was relatively contained, particularly with regard to the investigation of the neuropsychological impact of such surgical procedures. As such, the typical search criteria employed for selecting the studies which are later discussed was to include all available publications that related to any of the four stereotactic surgical procedures which are currently used worldwide in the treatment of intractable mental disorder.

1.1.2 Definition

Neurosurgery for Mental Disorder (NMD) has recently been defined in two leading UK reports as a neurosurgical procedure involving the destruction of brain tissue for the purpose of alleviating specific mental disorders. The procedure is described as a treatment of ‘last resort’, which may appropriately be considered for a small minority of individuals whose psychiatric symptoms have proved refractory to more

conventional forms of treatment (CRAG Working Group on Mental Illness, 1996; Royal College of Psychiatrists, 2000).

Until the last decade, such neurosurgical procedures were historically subsumed under the term 'Psychosurgery', an imprecise term which has incurred a variety of definitions. Central to the difficulty in accurately defining psychosurgery is the long-standing debate regarding precisely what constitutes a 'psychosurgery' procedure, in differentiation from any other 'neurosurgical' procedure (Feldman, Alterman & Goodrich, 2001). Historically, this distinction appears to have been determined by the abnormality, or otherwise, of the neural tissue involved. Thus, psychosurgery procedures were considered to involve surgical intervention performed on essentially 'normal' tissue, in comparison with other neurosurgical procedures which were generally thought to involve structurally 'abnormal' tissue. This definition however no longer appears helpful, as these distinctions are often ambiguous.

Continued use of the term 'psychosurgery' has been further condemned as being somewhat misleading, in that it maintains the inherent assumption that the procedures involved are distinct in some way from other neurosurgical procedures. The reality is that the modern use of neurosurgery for the alleviation of mental disorder is technically and conceptually comparable to many other forms of neurosurgery for example, in cases of intractable Parkinson's disease, chronic pain, and epilepsy. Therefore, the general conclusion that has been drawn from such debate suggests that it is the association of neurosurgical procedures with psychiatric

disorders, rather than disease status or surgical technique, which ultimately defines psychosurgery (Feldman et al, 2001; Sachdev & Sachdev, 1997).

Statutory definitions of psychosurgery throughout its 60 year history have been wide and varied. For example, in 1976 the World Health Organisation (WHO) defined it as, “selective surgical removal or destruction...of nerve pathways...for the purposes of influencing behaviour” (WHO, 1976). However, this broad definition has since been challenged on the grounds that behavioural change is no longer a primary indication for the use of such procedures. Ongoing difficulty continues to exist within the current climate regarding the interchangeable use of the term ‘psychosurgery’ with ‘lobotomy’ and ‘leucotomy’, referring to the early and controversial free-hand techniques which undoubtedly destroyed large sections of the frontal lobes, with often devastating consequences (Valenstein & Valenstein, 1986). Modern use of the term ‘neurosurgery for mental disorder’, in replacing that of ‘psychosurgery’, is therefore an attempt to distance the current and significantly more advanced stereotactic procedures from the earlier and now largely abandoned techniques of the past.

1.1.3 History of Development

In order to fully appreciate the social, ethical and clinical complexities associated with NMD in the current climate, it is necessary to understand the origins and context in which these interventions arose. Neurosurgical treatment for the alleviation of psychiatric symptoms has a long and somewhat controversial history which has seen a dramatic rise and fall in the use of such procedures. The earliest

recorded account of the experimental use of neurosurgical techniques was that conducted by Burckhardt in 1888, on a small series of individuals with intractable psychiatric illness. Although his work was not well received as a result of the associated adverse effects, he is regarded by many as the ‘founding-father’ of modern psychosurgery (Feldman & Goodrich, 2001).

Throughout the 1920’s and 1930’s research continued to investigate the anatomical correlates of mental illness through the observations of eminent neurosurgeons who reported the relief in psychiatric symptoms often observed following many of the common surgical procedures such as tumour removal. At the same time, progress in the field of primate research highlighted the behavioural effects of surgical intervention on frontal lobe functioning (Fulton & Jacobsen, 1935). The authors noted the calming effects achieved through the bilateral ablation of the frontal lobes of monkeys in whom they had previously induced a frustration response. Inspired by this, it was the work of the Portuguese neurologist Egas Moniz that brought psychosurgery into the professional and public domain. This was as a result of his interest in attempting to replicate with humans the calming effects such surgery was reported to have had in animal studies. Moniz theorised that under normal conditions, a network of nerve cells within the brain operated in an ever-changing fashion according to internal and external stimuli. He hypothesised that these networks became fixed in mental illness, resulting in disrupted thought processes which he believed could be eliminated by interrupting the pathways between the frontal lobe and the other regions of the brain.

After quickly abandoning his initial procedure which involved the injection of absolute alcohol into the frontal lobes, Moniz developed a new surgical procedure, namely the 'pre-frontal leucotomy'. This blind procedure was designed to sever the fibres connecting the frontal lobes with sub-cortical areas of the brain, through the use of a leukotome which enabled discrete 'cores' of white matter to be removed. Following the publication of his first 20 treatment successes (Moniz, 1936), the procedure was rapidly implemented worldwide. Acceptance of this procedure amongst the medical community, and the rapid rise in its use, can be explained in part by the political situation and societal attitudes of the early 1900's. As the number of individuals with mental illnesses rose within asylums, so too did the problems with overcrowding, inadequate staffing, and a sense of hopelessness associated with psychiatric problems. Available interventions included either long-term psychotherapy, or physical treatments such as insulin-induced coma, or electro-convulsive therapy, all of which proved unsuccessful for many. As a result, a new form of treatment which suggested that it could reduce or remove psychotic traits, produce calm behaviour, and re-integrate patients back into society, was welcomed by both political and social communities alike.

In 1937 Moniz coined the term 'psychosurgery', and published numerous articles and a book highlighting his experience of the leucotomies conducted to date. By 1949, he had achieved the height of critical acclaim in being awarded the Nobel Prize for his work on the prefrontal leucotomy. In spite of the lack of objective data or long term follow-up results, his work was continually welcomed and readily accepted in the medical field worldwide. Freeman and Watts (1942) were

responsible for the introduction and popularisation of their modified version of the surgical procedure in the United States, which became known as the 'standard pre-frontal lobotomy'. A number of modifications were made over the years that followed, including both open and closed procedures (Swayze, 1995). The main indications for the earlier neurosurgical procedures were schizophrenia, affective disorders, anxiety states, and Obsessive Compulsive Disorder (OCD) (Tooth & Newton, 1961).

The number of procedures soared throughout the 1940's and early 1950's, encouraged by efficacy studies claiming that 50 per cent of patients with affective disorders and 20 per cent with schizophrenia were well enough to be discharged following the leucotomy (Tooth & Newton, 1961). However, none of these studies were considered to have had satisfactory control groups. Nevertheless, reports estimate approximately 50,000 procedures having been carried out in the USA between 1936 and 1961 (Valenstein, 1980), and 10,500 in England & Wales alone by the mid 1950's (Swayze, 1995). It was however the popularity of the procedure at this point that inevitably culminated in its eventual decline.

Despite the seemingly encouraging outcome results, a growing awareness began to emerge regarding the adverse effects associated with these surgical procedures, the most commonly reported being haemorrhage, incontinence, epilepsy, and personality change. Such adverse effects were also undoubtedly minimised or under-reported (Feldman & Goodrich, 2001). Concerns also became raised within the medical community with regard to the absence of clearly defined indications for use, coupled

with a lack of critically appraised outcome information. In addition to a growing unease amongst those who were previously advocates of the procedures, it was the introduction of the first anti-psychotic drug, chlorpromazine in 1954 that provided the first effective pharmacological alternative to surgery. This growing backlash towards psychosurgery became evident in the significant drop in the number of procedures conducted throughout the 1950's and 1960's.

Despite the relative quietening of interest in the topic at this time, a new surge of publicity arose once again in the early 1970's as a result of fears that such procedures would be used politically as a means of social control, to treat aggressive individuals and urban violence in society. As a result of the heightened public and political interest, psychosurgery procedures became investigated and subsequently regulated by law, which resulted in severe restrictions in its use, to the point of prohibition in several countries. This procedural decline is evident in the total number of operations performed each year in the UK, which is noted to have fallen from 158 in 1974, to an average of 31 in the 1980's, and 23 in the early 1990's (CRAG Working Group on Mental Illness, 1996). Consequently, such neurosurgical procedures have, over time acquired a considerable amount of negative attention amongst professional and lay groups alike, discussion of which continues to evoke an emotive response from many.

Despite such discontent, research within the field of psychosurgery did however continue in the background. The introduction of stereotactic neurosurgical techniques allowing for closer precision targeting of lesion sites (Spiegel, Wycis,

Marks & Lee, 1947), and improvements in neuroimaging technology throughout the 1960's and 1970's, led to the development of a modern range of psychosurgery procedures which were far removed from their earlier counterparts in terms of current practice. A growing realisation emerged that despite modern advances in pharmacological and psychological therapies, a small group of individuals continue to exist whose conditions remain refractory to modern management. This has resulted in the continued availability and use of modern neurosurgical procedures in the case of intractable mental disorder.

1.1.4 Indications for Use

Early accounts of psychosurgery practice were largely concerned with the outcome of such operations on patients with affective disorders, OCD, and other anxiety states. In its earliest form, the diagnostic label was of lesser relevance in patient selection than the extent and severity of the functional impairment displayed. Initial outcome in the mid-1930's of surgery performed on individuals with schizophrenia was uninspiring, however further published outcomes of a more positive nature reignited interest in this patient group (Swayze, 1995). By the 1940's and 1950's, reports indicated that a large majority of the surgery performed was conducted on individuals with schizophrenia (Tooth & Newton, 1961). Despite the obvious methodological flaws of many of the early outcome studies, follow-up reports at this time did highlight significantly higher efficacy rates for affective disorders, in comparison to schizophrenia (Tooth & Newton, 1961). An emphasis on behavioural criteria was still in use in patient selection as late as the mid 1970's, with 6 units

within the British Isles reporting the use of psychosurgery in conditions associated with repeated violence (Barraclough & Mitchell-Heggs, 1978).

Indications for the appropriate use of neurosurgical procedures to address mental disorder have however changed significantly since its initial inception. Considerable refinement of patient selection criteria has been made over recent years in the light of available evidence regarding the clinical effectiveness of such procedures. An international consensus of opinion appears to exist, which recommends that the primary indications for the use of NMD today include treatment-refractory cases of major depressive disorder and OCD. A greater degree of disparity in opinion exists regarding intractable anxiety states and bipolar disorder.

Within the United Kingdom, a Good Practice Group was established in Scotland by the Scottish Office in 1993 with the aim of formally assessing the need for the provision of neurosurgery for the treatment of chronic and refractory mental disorder. Following consideration of the associated legal, ethical and clinical aspects, a report was subsequently published in 1996 (CRAG Working Group on Mental Illness, 1996), which recommended that NMD 'should continue to be available...only as a treatment for intractable obsessive compulsive disorder and affective disorders'. The report also highlighted that individuals should only be considered for NMD if their conditions are such that they have reached a level of severity and chronicity which has proved refractory to conventional psychological and psychiatric interventions. A subsequent report from the Neurosurgery Working Group of the Royal College of Psychiatrists (Royal College of Psychiatrists, 2000)

also acknowledged the need for continued NMD service provision for the small number of individuals with refractory depressive disorder and OCD, for whom it may be of benefit.

Contraindications to NMD generally include organic disorders, personality disorders, and drug or alcohol dependency. A primary diagnosis of schizophrenia is no longer considered an appropriate indication for surgery, however there is still debate regarding the measure of relief which may be gained in such individuals in which a substantial affective component is also present (CRAG Working Group on Mental Illness, 1996; Feldman et al, 2001; Rosenfield & Lloyd, 1999).

1.1.4 (a) Major Depressive Disorder

A diagnosis of major depression is typically arrived at through identification of characteristic clinical symptoms which include persistent low mood, loss of interest, lethargy, and disturbance of sleep and appetite. Major depressive disorder was identified in 1990 by public health experts as the fourth ranked cause of disability and premature death worldwide (Murray & Lopez, 1996). Single episodes of major depression are relatively rare, with the majority of affected individuals experiencing an average of four episodes during their lifetime (Angst, 1988). Epidemiological studies estimate that approximately 8 out of 10 people who experience a major depressive episode will have at least one additional episode, and even with successful treatment, there is a high risk of recurrence (Angst, Montgomery, Herbst & Paykel, 1992; Judd, 1997; Kupfer, Frank, Perel, Cornes, Mallinger, Thase et al, 1992). The

nature of the illness tends to increase in severity with each episode, thereby placing greater challenges on the available treatment options (Thase, 1992).

First line treatment in the case of depression includes an adequate trial of antidepressant medication, and/or cognitive behaviour therapy (Beck, 1967, 1976), which are successful in a large number of cases. However, despite significant advances in psychotherapeutic and pharmacological interventions, there remains a small group of individuals who appear to receive no symptom alleviation from any of the available interventions or their combinations, and for whom there appears to be little evidence or guidance regarding the best course of clinical management (Stimpson, Agrawal & Lewis, 2002). For such individuals, the psychological and social costs of such a chronic and debilitating illness are high, with an accentuated risk of suicide in high risk individuals, in the context of increasing despair following numerous treatment failures (Fawcett & Harris, 2001).

1.1.4 (b) Obsessive Compulsive Disorder

Obsessive Compulsive Disorder (OCD), categorised within the larger group of anxiety disorders, is typically defined by the presence of obsessions and/or compulsions that are of a level of severity, sufficient enough to result in significant distress or disruption to daily functioning. Obsessions include persistent thoughts, ideas or mental images which are experienced as being intrusive and unwanted, and which subsequently result in anxiety and distress. Compulsions take the form of intentional behaviours, often manifested as repetitive rituals or mental acts, which aim to prevent or reduce the anxiety associated with the obsessions.

Epidemiological studies suggest a lifetime prevalence rate of between 1 per cent and 3 per cent for OCD in the general population (Angst, 1994; Bebbington, 1998; Jenike, Baer & Minichiello, 1998). First line treatment typically involves pharmacotherapy, with serotonin reuptake inhibitors (SRI's), and/or an adequate course of behaviour therapy, consisting of exposure and response prevention. A large number of individuals will respond favourably to such interventions (Abramowitz 1997; Jenike, 1990; Veale, 1995), if not initially, but subsequently, following the trial of additional augmenting strategies including alternative pharmacological therapy, and/or individualised cognitive therapy interventions (Salkovskis, 1985). However, there are a minority of cases whose condition follows a chronic and unremitting course after all available treatment modalities have failed (Jenike, 1998). The considerable functional disability experienced in these cases often results in the requirement of in-patient management (Calvocoressi, McDougle, Wasylink, Goodman, Trufan & Price, 1993). It is for this severely ill group of individuals that NMD becomes a considered treatment option (Greist, 1990; Jenike, 1990). The exact size of this treatment-refractory population is as yet relatively unknown. The extreme nature of the disorder experienced by individuals who are considered for NMD is not considered to be representative of the general OCD population (Mindus, Rasmussen & Lindquist, 1994b).

1.1.5 Service Provision

Throughout the last two decades NMD has been performed consistently in a limited number of centres throughout the world, including the UK, USA, Australia, Sweden, Belgium, Spain, and the Netherlands. Each centre has typically focussed on a

limited type of procedure, for specific diagnostic groups (Malhi, Bridges & Malizia, 1997). A known complication of NMD services are their vulnerability to changes in key personnel, a factor responsible in the disruption or closure of several key centres over the last decade.

Despite the relatively small number of procedures conducted each year, NMD has attracted a disproportionately intense amount of scientific, public and political interest. In a bid to address the complex issues associated with this use of neurosurgical procedure, legislation has been introduced worldwide to govern what was perceived by many to be an inappropriately used intervention.

1.1.6 Regulation of Service Provision

Regulatory legislation varies within the United Kingdom. The introduction of the Mental Health (Scotland) Act 1984 provided legislative safeguards for patients for whom NMD was being considered. Section 97 of the Act states that the Mental Welfare Commission must be involved with all decisions regarding patients who are involuntarily detained. An independent medical practitioner appointed by the commission must certify the appropriateness of NMD in each case, and in addition to two lay people also appointed by the commission, certification must also be provided regarding the patient's understanding of the procedure and their ability to provide informed consent.

With regard to informal patients, that is those receiving inpatient treatment but who are not detained under the Mental Health Act, the above provisions do not apply.

There is currently no mandatory involvement with informal patients by the Mental Welfare Commission; instead, the decision to consent to NMD for these patients is at present their own choice. Current practice within the only Scottish centre to provide NMD is to involve the Commission in decisions regarding informal patients, in the same way that it would for detained patients, the only difference being that legal certificates are not issued. An evaluation of the issues involved in extending the legislative process currently only in use with detained patients, to informal patients, was considered in the recent Scottish Office report (Crag Working Group on Mental Illness, 1996). The resulting recommendation was that such legislation should be extended to include informal patients, and until such time the informal involvement of the Commission should continue.

The situation in England and Wales is essentially very similar to that in Scotland. Under Section 57 of the Mental Health Act (1983), the Mental Health Act Commission is involved in the certification procedures with regard to the appropriateness of surgery, and ability to consent, with the single difference being that these procedures refer both to detained and informal patients.

The position regarding the use of NMD with patients incapable of giving informed consent is less clear. Detained patients, who are deemed incapable of understanding and therefore consenting to the surgery, cannot lawfully be considered for NMD. As Section 97 in Scotland requires the patient's own consent, any other form of consent by proxy cannot be considered. In the case of informal patients thought to be incapable of giving informed consent, the legal provision of Section 97 does not

apply. Essentially, under common law it would be possible for the Scottish courts to appoint a tutor-dative to the patient with the power to consent to NMD if it was felt to be in the patient's best interests. As the legal position in England and Wales requires the patients own consent in both detained and informal cases, this issue would never arise, however it is at present theoretically possible in Scotland. The current position within the Scottish centre is that individuals considered to be incapable of providing informed consent are not offered NMD.

Similar legislative regulations exist in NMD centres worldwide. A number of countries such as Germany and Norway have entirely prohibited the use of NMD, whilst others have introduced such a degree of censure that in reality such procedures are rarely, if ever, carried out. A comparable process to that used in the UK, of obtaining patient consent and assessing the appropriateness of the procedure involved, has been made statutory in most states within both Australia and New Zealand (Hay & Sachdev, 1992). In North America the legal position tends to vary between states and provinces. In Europe, it is the responsibility of each individual European country to set its own guidelines.

1.2 NMD - Contemporary Neurosurgical Procedures

There are currently four stereotactic neurosurgical procedures which are preferentially used for the purpose of alleviating mental disorder worldwide: namely; anterior cingulotomy; anterior capsulotomy; subcaudate tractotomy; and limbic leucotomy (Malhi et al, 1997). The limbic leucotomy essentially involves the combination of lesions produced by the subcaudate tractotomy and anterior

cingulotomy. As such, there are effectively only three common lesion sites which are targeted by the four procedures. There are no longer any indications for the use of the standard pre-frontal leucotomy.

Each of the modern neurosurgical procedures are performed in a relatively standardised manner. Under local or more typically general anaesthesia, stereotactic techniques are employed. This involves fixing the patients head in a metal frame which, under the guidance of computer tomography and/or magnetic resonance imaging, is subsequently used as a reference point from which the depth and angle of the probe to be inserted can be determined. Such scanning techniques can subsequently be used post-operatively to confirm the placement and size of the lesions. In each surgical procedure, bilateral targets are identified on each hemisphere, and a selective number of burr holes are created depending on the procedure. Lesions have typically been created by means of surgical resection, radioactive rods, radiofrequency probes, or cryogenic probes. The majority of contemporary procedures involve radiofrequency probes, in which the tip of the uninsulated probe is heated to a level able to produce small coagulation lesions in the target area, with the minimum of disruption to surrounding tissue.

1.2.1 Anterior Cingulotomy

The Anterior Cingulotomy was initially performed as an open procedure involving the resection of anterior fibres of the cingulate gyrus, the use of which was first reported in 1952 (Whitty, Difffield, Tow & Cairns, 1952), and later popularised by Ballantine and colleagues (Ballantine, Bouckoms, Thomas & Giriunas, 1987;

Ballantine, Cassidy, Flanagan & Marino, 1967). The advent of stereotactic techniques enabled modifications to the procedure resulting in the severing of the anterior cingulate fibres, as opposed to their excision, with the aim of interrupting the tracts between the frontal and thalamic regions, thereby disrupting the medial limbic circuit (see Figure 1). Over the last two decades, the cingulotomy has been the most widely used procedure in North America, initially developed for use in alleviating chronic pain (Foltz & White, 1962), and later modified for use with affective disorders, anxiety states and OCD. This procedure is now performed within the Scottish centre.

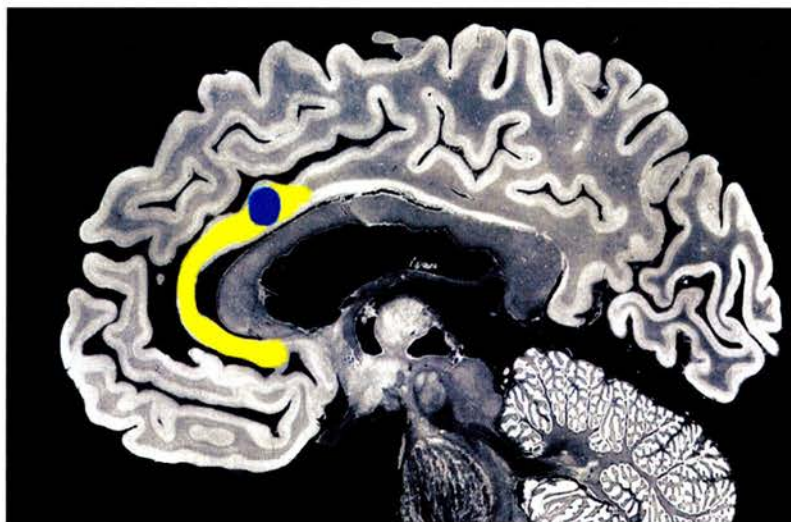


Figure 1. Lesion site for Stereotactic Anterior Cingulotomy
(Reproduced with permission from Matthews & Eljamel, 2003)

1.2.2 Anterior Capsulotomy

The Anterior Capsulotomy involves the creation of lesions in the anterior limb of the internal capsule, aimed at interrupting the pathways between the orbito-frontal cortex and thalamic nuclei as they pass through the internal capsule (see Figure 2). This technique was developed by Talairach and colleagues in light of post-mortem studies of previously successful lobotomy operations which were also noted to display a degree of degeneration of the thalamic nuclei (Talairach, Hecaen & David, 1949). Additional inspiration for the procedure came from other anatomical studies. These highlighted that connections between the orbito-frontal cortex and the thalamus passed through the internal capsule between the head of the caudate nucleus and the putamen. The anterior capsulotomy is currently performed in Sweden, Scotland and Wales (CRAAG Working Group on Mental Illness, 1996).

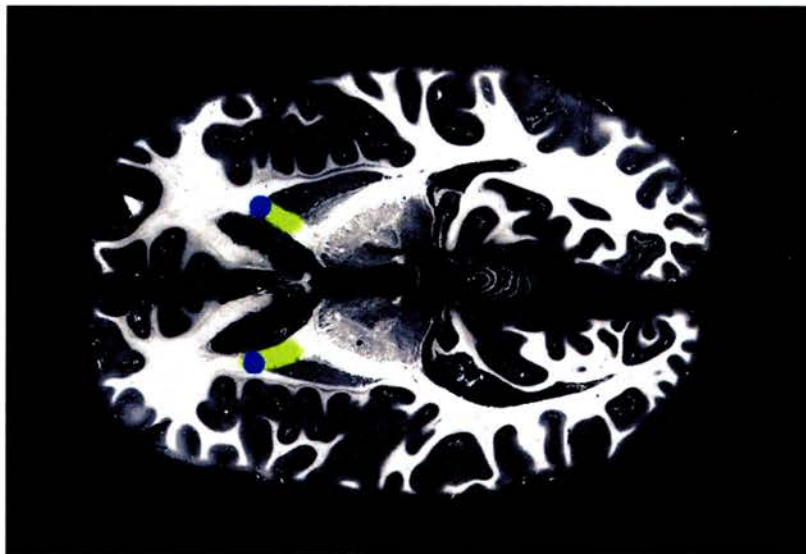


Figure 2. Lesion sites for Stereotactic Anterior Capsulotomy
(Reproduced with permission from Matthews & Eljamel, 2003)

1.2.3 Subcaudate Tractotomy

The Subcaudate Tractotomy was developed by Knight (1965) in London, and was based on Scoville's open procedure of 'selective orbital undercutting' (Scoville, 1960). In the modern procedure, lesions were initially created through the insertion of radioactive rods or beads, placed in the posterior part of the orbito-frontal cortex which passes below the head of the caudate nucleus. The rods were inserted through bilateral burr holes in the frontal bone of the forehead, and aimed to disrupt the pathways between the supra-orbital section of the frontal lobe and the limbic system. These lesions disrupt the same fronto-thalamic pathways as in the anterior capsulotomy. Since 1996 the lesions created in the modern use of this procedure have been made through the stereotactic placement of radiofrequency probes. Although initially an extremely popular procedure, due to the closure of the NMD centre in London, it is now no longer performed within the UK.

1.2.4 Limbic Leucotomy

The Limbic Leucotomy was developed by Kelly and colleagues in the UK, with the aim of combining the therapeutic effects of both the subcaudate tractotomy and the anterior cingulotomy (Kelly, Richardson & Mitchell-Heggs, 1973). The authors hypothesised that the combined effect of this procedure would prove more effective in reducing symptoms than either procedure on its own. Again, the aim was to interrupt the fronto-limbic connections with lesions created in both the ventro-medial quadrants of the frontal lobes, as well as in the cingulum bundle. This subsequently involved damage to a larger area of neural tissue than was associated with each of the

other individual operations. The limbic leucotomy is the least commonly performed operation currently in use, and is no longer performed within the UK.

1.2.5 Choice of Procedure

One of the most consistent criticisms in the field of psychosurgery is that regarding the relative lack of evidence comparing the efficacy rates of each of the contemporary procedures. The current evidence which does exist appears to suggest very similar success rates for all four operations (Jenike, 1998). At present there is no international consensus on the optimal site targeted for any specific disorder.

1.3 NMD – Theoretical Basis

1.3.1 Mechanisms of Change

At present, there continues to be a significant amount of uncertainty surrounding the theoretical underpinning on which NMD is based (Sachdev & Sachdev, 1997). There is as yet no clear agreement regarding the exact underlying mechanisms by which these neurosurgical procedures exert their effect. The fact that existing data reports comparable degrees of efficacy for each of the modern procedures has only acted to complicate this issue. Numerous explanations have been proposed to account for the consequential clinical responses observed following such procedures, and can broadly be divided into those which are directly related to the surgical effects, and those which appear unrelated to such specific influences.

As a result of the relative uncertainty as to the precise mechanisms by which NMD works, the possibility of factors such as placebo effect have previously been

discussed in the literature. The possibility of a placebo response has been raised particularly on occasions where dramatic early responses to surgery have been observed, a time when expectations for improvement are high. Indeed, initial impressive responses in the acute period following surgery which have not subsequently been maintained at longer term follow-up have previously been reported (Poynton, Bridges & Bartlett, 1988). The nature of NMD requires that adequate trials of all other effective psychological and pharmacological treatments have been implemented before proceeding towards consideration for NMD. As such, it is essentially considered to be a treatment of last resort. Consequently, this can engender in many patients and their families a great sense of hope and anticipation of improvement in the period following these procedures. It would appear possible, therefore, that this positive pre-operative investment in the treatment may serve to influence the post-operative outcome, at least in the acute stages.

In relation to the previous issue, reports regarding the effect of sham procedures in the field of NMD are understandably scarce, given the severity of the disorders involved and the ethical objections it raises. There is no evidence from the case studies which do exist to support sustained clinical improvement in the longer term. Direct attempts have been made in two studies, in which small groups of individuals were operated on but did not receive the required lesions (Balusabramianian, Kanaka & Ramanujam, 1973; Livingston, 1953). In neither group did improvement occur. Both studies were also conducted on patients whose primary diagnoses would no longer be considered a suitable indication for surgery. A further single case study was reported by Corkin and colleagues, who documented their experience of one

individual amongst a series of patients undergoing treatment by anterior cingulotomy (Corkin, Twitchell & Sullivan, 1979). This single case was discovered during surgery to have such atypical brain anatomy that the required lesions could not be performed. Post-operatively, the patient was informed that the procedure had been modified and had been a success. The authors reported some functional improvement in the patient's condition for a period of several months after the operation; however, this effect was not reported to have been sustained in the longer term. At the same time, Cosyns & Gybels (1979) similarly reported no improvement effect following a sham operation on an individual with OCD.

Other non-surgical influences which have been considered in the explanation of general post-operative improvement include spontaneous remission, which would seem highly unlikely given the enduring nature and severity of the disorders involved. Evidence also suggests that there is little support for the case of spontaneous remission in, for example, treatment-refractory OCD (Rasmussen & Tsuang, 1984). Significant changes in life circumstances following surgery such as the range and intensive nature of some post-operative rehabilitation input, has also been proposed as a potentially contributing factor in accounting for some of the positive clinical response noted (Corkin et al, 1979). There are also reports within the literature which highlight the improvement in efficacy of psychological and pharmacological therapies following surgery, thereby suggesting that surgery may act as an augmenting factor in a proportion of cases (Cosyns & Gybels, 1979; Kelly, 1980).

It is also possible however that any general post-operative improvement may occur as a direct result of the surgery itself. Evidence exists to support specific effects following the destruction or interruption of pathways between interconnected brain regions, through observation of neurobiological changes following NMD procedures. Neuroendocrine, neuroanatomical, and neurochemical changes have been observed (Malizia, 1997; Marino & Cosgrove, 1997). In order to understand the recent advances in theoretical hypotheses, an appreciation of the traditional rationale for conducting such physical interventions in the current manner is required.

1.3.2 Theoretical Rationale

Historically, the selection of lesion sites in psychosurgery was largely influenced by the theory of Papez (1937), who proposed the concept that certain anatomical correlates may be involved in the process of human emotion. Papez' theory hypothesised that emotional stimuli passed through a neural circuit connecting the frontal lobes with the cingulate gyrus, hippocampus, hypothalamus, and the anterior thalamic nuclei. This was based on the deduction that an interconnecting loop must be present between the hypothalamus, which had been noted to play an important role in the expression of emotion, and higher cortical areas: in particular the frontal lobes, given the reciprocal effect observed between emotion and thought processes. The term 'limbic system' was first coined by MacLean in 1952, who later proposed a rationale for widening the number of structures considered to constitute the limbic system (MacLean, 1955). Since then, increasing numbers of models regarding the cerebral processes underlying affective experience have been proposed.

The underlying rationale was that the interruption of any of the proposed pathways between the limbic structures and the frontal lobes may inhibit the effect of the frontal cortex by blocking the input to this area. By interrupting the higher-order processing typically involved with the frontal cortex, it was assumed that this would result in the alleviation of psychiatric symptoms (Marino & Cosgrove, 1997). This original reasoning for the precise placement of neurosurgical lesions in NMD was based on a more limited understanding of brain function and a considerable amount of anecdotal evidence. However, recent neuroimaging research has provided further evidence to support the previously empirically based choice of specific lesion sites.

Through examination of changes in brain activity, a rapidly accruing body of evidence has confirmed that neurobiological changes do occur within these traditionally proposed regions of the brain in cases of both major depressive disorder and OCD, the two principal indications for consideration for treatment by NMD. Whilst the exact relationship between the physiological status and psychological symptoms is as yet unclear, it has provided a tentative theoretical basis which is relevant in consideration of the therapeutic effects of NMD. Therefore, in attempting to delineate how it works, a level of understanding regarding the underlying pathophysiology of the disorders involved is necessary.

1.3.3 Neurobiological Correlates in Depressive Disorder

Recent structural imaging studies provide initial evidence for the presence of structural brain changes in patients with mood disorders (Ketter, Bench, George, Kimbrell & Post, 2001; Soares & Mann, 1997; Steffans & Krishnan, 1998).

Increased white matter hyperintensities have been reported, in addition to focal changes in the prefrontal cortex, basal ganglia and cerebellum. Functional imaging studies have also demonstrated abnormalities in depressed patients through measurement of cerebral blood flow and glucose metabolism. Focal deficits involving anterior cortical, paralimbic, and subcortical regions have been noted in primary depression, with the majority of studies demonstrating decreased activity in the former areas, most frequently in the prefrontal cortex and cingulate gyrus (Ketter et al, 2001). However, a number of studies have also demonstrated increased cerebral activity in the same regions of the brain in which the previous decreases were noted (Drevets, Videen, Price, Preskorn, Carmichael & Raichle, 1992; Goodwin, Austin, Dougall, Ross, Murray, O'Carroll et al, 1993; Hornig, Mozley & Amsterdam, 1997).

1.3.4 Neurobiological Correlates in OCD

Structural imaging studies using mMRI have reported subtle volumetric abnormalities in the caudate nucleus in OCD (Rauch & Baxter, 1998). A growing body of research based on functional imaging studies has also implicated specific brain regions with increasing consistency (Kang, Kwon, Kim, Youn, Park, Kim, et al, 2003; Rauch & Baxter, 1998; Trivedi, 1996). Evidence suggests that functional changes occur in OCD, typically by means of increased activity in the orbitofrontal cortex, anterior cingulate, and caudate nucleus (Baxter, Phelps, Mazziotta, Guze, Schwartz & Selin, 1987; Baxter, Schwartz, Mazziotta, Phelps, Pahl, Guze et al, 1988; McGuire, Bench, Frith, Marks, Frackowiak & Dolan, 1994). These changes are reported to be exacerbated during symptom provocation, and normalised following

successful treatment, including pharmacotherapy and behaviour therapy (Baxter, Schwartz, Bergman, Szuba, Guze, Mazziotta et al, 1992; Benkelfat, Nordahl, Semple, King, Murphy & Cohen, 1990). As is the case in neuroimaging studies in depression, however, there is some inconsistency in the reported findings, with additional studies demonstrating underactivity (Saxana & Rauch, 2000). It has been suggested that such discrepancy in results may be the result of differences in the varying nature of disorder subtypes and sub-structures under study, and also technological and methodological differences across studies (Ebert & Ebmeier, 1996; Trivedi, 1996).

Taken together, these recent neuroimaging studies have implicated several of the key regions of the brain, previously outlined in the model proposed by Papez (1937) in the underlying pathogenic mechanisms suggested to be involved in both disorders. These findings have led to the advancement of increasingly more detailed neurobiological models for both depression and OCD (Alexander, DeLong & Strick, 1986; Baxter, 1990; Insel, 1992; Modell, Mountz, Curtis & Greden, 1989; Rapoport, 1990). These models propose that dysfunctional neuronal circuits underlie the presence of depression and OCD (Sachdev & Sachdev, 1997). Each of the four modern NMD procedures targets specific areas within these hypothesised circuits, between the limbic system and its connections with the frontal cortex. To date however, despite advancing our understanding of the possible underlying neuroanatomical correlates, these studies are still considered to be in their infancy, and continue to raise as many questions, as they do answers (Ovsview & Frim, 1997; Trivedi, 1996).

Modern neuropsychological research has also provided evidence in support of the physiological findings which have highlighted the involvement of specific brain regions in both OCD and depressive disorder. Traditionally, cognitive impairment observed in patients with psychiatric disorders was attributed to the severity of their psychological symptoms. More recently an increasing evidence base has suggested that conditions such as depression and OCD may be associated with abnormal brain functioning, at least in a proportion of cases.

1.3.5 Neuropsychological Deficits in Depressive Disorder

Neuropsychological studies in depression have reported a broad range of cognitive deficits of variable nature and severity. Those studies focussed more predominantly on groups of older adults (>65 years) have consistently reported impairments across a range of cognitive functioning (Abas, Sahakian & Levy, 1990; Beas, Sahakian & Levy, 1996; Brown, Scott, Bench & Dolan, 1994). Investigation amongst the younger age groups has resulted in more ambiguous results: some studies reporting specific deficits involving, for example, motor speed, attention, memory, and executive function (Franke, Maier, Hardt, Frieboes, Lichtermann & Hain, 1993; Golinkoff & Sweeney, 1989; Ilsley, Moffoot & O'Carroll, 1995; Purcell, Maruff, Kyrios & Pantelis, 1997); and others failing to find any cognitive impairment (Albus, Hubmann, Wahlheim, Sobizack, Franz & Mohr, 1996; DeLuca, Johnson, Beldowicz & Natelson, 1995; Martin, Oren & Boone, 1991). It has been suggested that such variability may result from a number of factors including the heterogeneity of depression, as well as individual patient characteristics such as age, hospitalisation, and the effect of medication. In much of the research investigating cognitive

function in depression, such factors have rarely been statistically controlled. A recent exception to this is a study conducted by Porter and colleagues who examined neuropsychological function in a group of younger adults (<65 years) with depression, whilst controlling for the potentially confounding effects of medication (Porter, Gallagher, Thompson & Young, 2003). The authors concluded that significant cognitive impairment was demonstrated across a range of functions in the depressed group in comparison with matched healthy controls, and proposed that such impairment could potentially be used as a marker of brain dysfunction in depression.

1.3.6 Neuropsychological Deficits in OCD

Neuropsychological studies have similarly reported an association between neuropsychological impairment and OCD, when compared to control groups, and those with other anxiety disorders. The proposed pattern of deficits has been suggested to differ according to the specific subtype involved, and the related level of symptom severity and chronicity (Head, Bolton & Hymas, 1989; Okasha, Rafaat, Mahallawy, El Nahas, El Dawla, Sayed et al, 2000). A recent review of neuropsychological studies in OCD highlighted the presence of specific, but not global impairment in executive functioning, with the most striking results evident on tests requiring organisational strategies (Greisberg & McKay, 2003). OCD patients have also been noted to display deficits in cognitive set-shifting abilities, selective attention, mental flexibility, and visuospatial ability (Boone, Ananth, Philpott, Kaur et al, 1991; Head et al, 1989; Okasha et al, 2000). Less consistent findings have been reported regarding memory deficits. Where memory impairment has been observed

however, performance is reportedly more adversely affected if the task is non-verbal, and noted to encompass an organisational element (Christensen, Kim, Dysken & Hoover, 1992; Greisberg & McKay, 2003; Savage, Baer, Keuthen et al, 1995).

1.3.7 Correlation between Neuroanatomy & Neuropsychology

Significant correlations between measures of global cognitive function and decreased regional cerebral blood flow (rCBF) in the medial prefrontal cortex have been reported in cases of depression (Bench, Friston, Brown, Frackowiak & Dolan, 1993; Dolan, Bench, Friston, Brown, Scott & Frackowiak, 1992; Dolan, Bench, Brown, Scott, & Frackowiak, 1994). Similarly, significant correlations have also been reported between changes in glucose metabolic rates, in areas involving the neural circuits currently implicated in OCD, and improvement in specific neuropsychological sub-tests following treatment (Kang et al, 2003). These findings provide further tentative evidence in support of an association between the cognitive deficits observed in these disorders, and an underlying abnormality in specific brain regions.

Summary

It is likely that the clinical effects reported following treatment by NMD are a combination of both surgical and non-surgical factors. The underlying rationale regarding the placement of such specific lesions has been supported by neurophysiological and neuropsychological evidence which has implicated involvement of key regional areas of the brain in the two conditions for which NMD is currently indicated.

1.4 NMD – Efficacy

1.4.1 Methodological Limitations

Any evaluation of the efficacy of NMD procedures could be considered to be misleading if conducted without an adequate appreciation of the considerable methodological issues which are inherent within this field of research.

The distinct lack of well-controlled research studies is one of the most striking and highly criticised aspects within this evidence base. This is largely due to the considerable practical and ethical objections which have been raised regarding the use of non-surgical or sham control groups (Binder & Iskandar, 2000; Jenike, 1998; Kartsounis, Poynton, Bridges & Bartlett, 1991). This has resulted in the absence to date of any prospective double-blind randomised controlled trial; the method typically aspired to in studies of clinical efficacy. In light of this, the majority of published NMD outcome research consists of single-centre studies of a chosen surgical procedure, on a chosen diagnostic group, typically involving a small cohort of participants. The latter point regarding sample size is of considerable salience to this population group given the rarity of such intractable mental disorders, the small number of centres of expertise available to offer such ablative neurosurgical procedures, and the typically long period of follow-up which is required to assess what is often a very gradual change in behaviour.

Notwithstanding these inherent obstacles however, there are a number of common methodological failings which apply to much of the research conducted, particularly in earlier studies on which some of the current estimates of efficacy are still based.

Frequently, heterogeneous diagnostic groups have been pooled together in the evaluation of outcome of a specific procedure. Whilst this would certainly increase the statistical power of the study, it also introduces the confounding effect of subgroup differences. Similarly, many of the studies including larger groups of participants have been comprised of individuals who were operated on often decades apart, thereby introducing the confounding effect of different diagnostic classification systems, availability of previous psychological and pharmacological therapies, and therefore perhaps a different type of refractory illness.

Many of the studies to date have been retrospectively designed, at times resulting in the absence of adequate pre-operative data with which to compare results. More detailed investigation revealed that the 'pre-operative' ratings quoted in a sample of these studies involved a retrospective estimation of performance made either by the patient themselves, by the referring agents, or from information recorded in individual case notes (e.g. Irle, Exner, Thielen, Weniger & Ruther, 1998; Nyman, Andreewitch, Lundback & Mindus, 2001; Ruck, Andreewitch, Flyckt, Edman, Nyman, Meyerson et al, 2003). In other cases, inter-individual, pre- and post-operative comparisons have been made with separate groups of individuals (Cumming, Hay, Lee & Sachdev, 1995; Nyman et al, 2001).

The issue of bias in many of the studies must also be taken into consideration. There is a distinct lack of objective, critical evaluation by independent investigators amongst the literature, with the centres responsible for patient selection and surgery, often the same centres who conduct the outcome research (Binder & Iskandar, 2000;

Jenike, 1998). However, this is often the result of having so few clinicians with expertise of this specialised population group. The subjective nature of several of the outcome measures employed has also been criticised, with an absence of information regarding their documented reliability and validity (Jenike 1998). There is similarly little information reported with regard to post-operative rehabilitation (Mindus, Rauch, Nyman, Baer, Edman & Jenike, 1994a), and often considerable variability in the length of follow-up period on which outcome assessments have been based.

The issue of bias may also be relevant in consideration of the patient groups under study, which for often justified reasons do not comprise entire consecutive referrals, but instead represent a select patient group. A common criticism of much of the earlier research was the bias towards reporting positive effects following surgery which were often lacking in detail, and minimising or under-reporting adverse effects (Hay, Sachdev, Cumming, Smith, Lee, Kitchener et al, 1993; Jenike, 1998). Whilst this has been addressed in the majority of modern studies, there does however still appear to be a general lack of discussion regarding additional potentially contributing factors which may account in part for any success noted following such operations.

Comparison of the efficacy rates across studies is often extremely difficult in light of the non-standardised approach taken to diagnostic classification, patient selection criteria, evaluation of previous treatment adequacy, type and nature of surgery implemented, post-operative rehabilitation, outcome criteria, psychometric measures, and methodological design (Diering & Bell, 1991; Fenton, 1998). There are also no modern prospective comparisons of the main contemporary procedures, given the

fact that most NMD centres favour one procedure over another, and typically proceed to develop their expertise in that field. This has resulted in several small clusters of reports regarding each of the four main procedures.

Summary

There are a number of methodological concerns which affect many of the studies on which efficacy figures for NMD are based. Such limitations must therefore be taken into consideration in any informed evaluation of outcome.

1.4.2 Controlled Studies

There exists a small number of controlled studies of retrospective design from which the general outcome of several neurosurgical procedures has been reported. The majority of these studies are based on the comparison between an operated group of individuals with intractable OCD, and a matched non-surgical control group.

An early report on the non-stereotactic procedure, modified leucotomy, reported a significantly better outcome across a five year follow-up period for a surgery group of 24 OCD patients, when compared to 13 matched non-surgical controls (Tan, Marks & Marset, 1971). This research was based on the design of a previous study (Marks, Birley & Gelder, 1966) which reported significant reductions over time in the severity of general anxiety and phobias in a surgery group treated with the former procedure, when compared to a matched non-surgical control group. Hay and colleagues provided further support for the positive effects of a mixed range of stereotactic neurosurgical procedures following the comparison between a subgroup

of OCD patients with 10 matched non-surgical controls (Hay et al, 1993). Thirty per cent of the surgery group were reported to have demonstrated significant improvement at follow-up, whilst none of the control group demonstrated remission of symptoms for a period greater than six months. More recently, Cosyns and colleagues reported a significant reduction in the level of target symptoms in a mixed operative group of 21 patients with intractable OCD, when compared to a group of 7 matched control patients who had refused to consent to surgery despite their suitability for it (Cosyns, Caemaert, Haaijman, vanVeelen, Gybels, vanManen et al, 1994).

1.4.3 Global Outcome Studies

In evaluating the general outcome following NMD, there exist several review articles which have attempted to consolidate the available evidence base. One of the greatest challenges in combining the results however has been the wide variability of global outcome measures employed across the published literature. One of the most widely accepted and readily modified measures of clinical outcome is that of the post-operative global rating scale initially developed by Pippard (1955). This measure comprises a five point scale which ranges between the highest levels which indicate that an individual is either free from the symptoms which led to surgery or much improved, through to the presence of slight improvement but still requiring medication, to the bottom levels in which an individuals condition is considered to be either unchanged or worse than their pre-operative condition. Use of such a scale has allowed comparisons across diagnostic groups and procedures.

Estimates regarding the global outcome of a range of neurosurgical procedures, pertaining to a range of diagnostic categories, are available from a handful of consolidated reviews. An initial review of studies conducted between 1960 and 1976 reported the outcome of both stereotactic and non-stereotactic lesions in a total of 258 patients with OCD (Smith, 1977). An overall total of 84 per cent were reported to have improved, with significant improvement noted in 55 per cent. Kiloh and colleagues subsequently reviewed 25 studies representing a total of 456 OCD patients who had undergone a variety of neurosurgical procedures of both a stereotactic and non-stereotactic nature between 1961 and 1980 (Kiloh, Smith & Johnson, 1988). The authors reported significant improvement in 58 per cent, with a further 27 per cent achieving moderate improvement. Most recently, Waziri (1990) obtained similar results following a consolidated review of 300 OCD patients treated with a range of NMD procedures between 1961 and 1988. An aggregated total of 38 per cent were reported to be symptom-free following surgery, with moderate improvement noted in 29 per cent, and slight improvement in 20 per cent.

A similar picture exists in cases of major depressive disorder. Kiloh and colleagues reviewed the global outcome of 727 patients across 21 studies, and reported significant improvement in 63 per cent, with a more moderate improvement noted in a further 22 per cent (Kiloh et al, 1988).

The most recent review regarding the global outcome of the modern stereotactic neurosurgical procedures was provided in a recent British report (Royal College of Psychiatrists, 2000). With regard to the outcome of stereotactic operations in the

case of OCD, the report outlined a total of 28 published studies representing 570 patients. The authors did however highlight the variability of outcome measures employed across the studies and the often inadequate methods of reporting used when disseminating such data. As a result, a reliable comparison of outcome data based on the Pippard post-operative rating scale (Pippard, 1955), or some modification of it, was possible only in a total of 6 studies representing 198 patients (Bingley, Leksell, Meyerson & Rylander, 1977; Burzaco, 1981; Fodstad, Strandman, Karlsson & West, 1982; Kelly, 1980; Strom-Olsen & Carlisle, 1971; Tippin & Henn, 1982). Similar to the earlier report from Waziri (1990), results suggested approximately one-third of patients achieved symptom-free status following surgery, another one-third displayed moderate improvement with minor residual symptoms, and a further 23 per cent showed slight improvement. In the case of depressive disorders, 3 studies from a total of 11, representing 189 patients, provided outcome information based on a comparable 5-point scale (Goktepe, Young & Bridges, 1975; Kelly, 1980; Strom-Olsen & Carlisle, 1971). Results indicated that one-third of depressed patients were symptom free following surgery, 23 per cent displayed only minor symptoms, and 22 per cent displayed slight improvement with moderate residual symptoms.

1.4.4 Symptom-based Outcome Studies

In light of the criticism associated with global clinical categories, the relative merit regarding the use of alternative symptom-based rating scales has been discussed in the literature. It has been suggested that the replacement of global measurements with symptom rating scales would further narrow opportunities for comparison of

outcome across diagnostic groups, and may restrict the measurement of what may be a longer term recovery process, to a single event measurement (Bridges, Bartlett, Hale, Poynton, Malizia & Hodgkiss, 1994; Hodgkiss, Malizia, Bartlett & Bridges, 1995).

Evidence has also suggested however that global outcome scales, such as the Pippard post-operative scale, do correlate highly with self-report symptom measures such as the Wakefield Depression Score (Snaith, Ahmed, Mehta et al, 1971) and the Taylor Manifest Anxiety Scale (Taylor, 1955) (Goktepe et al, 1975). As such, in the largest outcome studies in depression, the majority of which involve treatment by subcaudate tractotomy, outcome measurement has typically focussed on the use of global clinical categories believed to encompass a combination of both symptomatic and social outcome aspects (Goktepe et al, 1975; Hodgkiss et al, 1995; Strom-Olsen & Carlisle, 1971).

Increasingly however, modern evaluation of outcome following NMD procedures is including symptom-specific measures in addition to the more global rating scales, with similar outcome figures reported. For example, in the case of OCD recent studies, which have included reliable symptom measures such as the Yale Brown Obsessive Compulsive Scale (Y-BOCS) (Goodman, Price, Rasmussen, Mazure, Fleischmann, Hill et al, 1989), have reported significant reductions in target symptoms of up to 50 per cent following a range of surgical procedures (Baer, Rauch, Ballantine, Martuza, Cosgrove, Cassem et al, 1995; Hay et al, 1993; Irle et al, 1998; Jenike, Baer, Ballantine, Martuza, Tynes, Giriunas et al, 1991).

1.4.5 Differential Efficacy Rates according to Procedure

There are obvious methodological flaws inherent in the previous method of retrospectively collating and comparing results from studies which include assessment across diagnostic groups and surgical procedures, with differing sized population groups and length of follow-up period. The converse approach would be to conduct prospective comparative studies with homogeneous diagnostic patient groups, an area in which there is currently a distinct lack of published evidence. At present the type of neurosurgical procedure a patient receives is largely dependant on the centre performing the operation and the nature of their psychiatric condition. Therefore, one of the most fundamental issues within NMD research which continues to remain unresolved is that regarding the lack of understanding of the differential outcome resulting from the various neurosurgical procedures. Relatively few studies have attempted to make direct comparisons between such procedures. These studies will now be reviewed in line with available evidence to support the use of each individual procedure, in cases of both depressive disorder and OCD.

1.4.5 (a) Anterior Capsulotomy

The few comparative accounts which do exist have typically focussed in particular on investigating the efficacy of anterior capsulotomy versus anterior cingulotomy. Such studies would suggest a relatively superior role for anterior capsulotomy in the treatment of intractable OCD. One such prospective study was that carried out by Kullberg (1977), who compared the effects of capsulotomy and cingulotomy procedures, performed alternately in a total of 26 operations. The patient group consisted of intractable OCD and non-obsessional anxiety diagnoses. The author

concluded that anterior capsulotomy provided more sustained symptomatic relief in comparison to anterior cingulotomy. It is of note that there were more cases of OCD in the former group. However, this achievement appeared to be at the expense of more marked transient post-operative disturbance and notable personality change.

Fodstad and colleagues conducted a prospective randomised clinical trial in a group of 4 patients experiencing intractable OCD (Fodstad et al, 1982). Two patients underwent anterior capsulotomy, and the remaining two anterior cingulotomy. Neuropsychological and psychiatric assessments were conducted both pre- and post-operatively, on the basis of which the authors claimed increased efficacy for the capsulotomy procedure in treating obsessional disorders. More recently, Sachdev and Hay (1996) produced evidence in support of the beneficial effects of capsulotomy for cases of OCD, in comparison to lesions restricted to the cingulate tracts or orbitomedial area. The small number of participants must however be taken into account in interpreting the results of these studies.

Evidence from a recent meta-analysis of eight case series has provided further support for the positive outcome reported in obsessional disorders following treatment by anterior capsulotomy (Mindus & Meyerson, 1995). Similarly, in a consolidated review of outcome studies evaluating a range of surgical procedures used to treat OCD and other anxiety disorders, Waziri (1990) also concluded greater post-operative outcome following anterior capsulotomy.

There appears to be only one published outcome study offering evidence regarding the use of anterior capsulotomy in depressive conditions. Herner (1961) reported a 'good' improvement rate of 53 per cent in a depressed group of 19 patients, with 'fair' improvement in a further 21 per cent, and 'poor' outcome in 26 per cent after a follow-up period of up to 24 months. Generalisation from the results of this study must however be viewed with great caution. Not only was the study conducted over forty years ago, but the composition of the depressed group on which these results were based was extremely heterogeneous, including cases of psychosis, neurosis and epilepsy.

1.4.5 (b) Subcaudate Tractotomy

There is a distinct lack of published research investigating the comparative efficacy of neurosurgical procedures in cases of depression. The evidence which does exist has typically focussed on outlining the global outcome following stereotactic subcaudate tractotomy which accounts for approximately two-thirds of the procedures conducted in cases of intractable depression. Evidence would appear to suggest a slightly higher rate of improvement in treating depressive conditions, in comparison to OCD.

Strom-Olsen & Carlisle (1971) initially reported higher outcome results following subcaudate tractotomy in patients with depression, with complete recovery or significant improvement noted in 56 per cent of this group, as compared to 50 per cent in the OCD group. A further study of 134 patients of varying diagnoses also reported greater improvement rates in those with depressive illness, with 68 per cent

reported to be recovered or significantly improved following subcaudate tractotomy, compared to 50 per cent in the OCD group (Goktepe et al, 1975). More recently, Hodgkiss and colleagues evaluated the outcome of 249 patients of mixed diagnoses, who underwent subcaudate tractotomy within the UK, between 1979 and 1991 (Hodgkiss et al, 1995). At 12 month follow-up the greatest outcome was noted in the depressed group, with 34 per cent reported to be recovered or significantly improved. However, despite the trend towards superiority in the depressed group, the difference in outcome between the diagnostic groups was not significant on this occasion.

1.4.5 (c) Anterior Cingulotomy

Earlier research on the outcome following anterior cingulotomy in cases of treatment-refractory depression highlighted significant post-operative improvement in approximately 40 per cent of cases. Whilst it is not possible to make a useful comparison of outcome across the available evidence base, the published literature has suggested a relatively comparable rate of improvement in cases of OCD and depressive disorder (Ballantine et al, 1987; Corkin et al, 1979; Martin, McElhaney & Meyer, 1977; Spangler, Cosgrove, Ballantine, Cassem, Rauch, Nierenberg et al, 1996; Winston, 1979). Recent evidence from two prospective studies have reported similar response rates in patients with intractable OCD; one study reporting that 32 per cent of patients who had undergone anterior cingulotomy met criteria for treatment response at an average follow-up time of 32 months (Dougherty, Baer, Cosgrove, Cassem, Price, Nierenberg, 2002), and the other, a 43 per cent response rate at 12 month follow-up (Kim, Chang, Koo, Kim, Suh, Park et al, 2003).

1.4.5 (d) Limbic Leucotomy

Evidence with regard to the treatment of intractable depressive disorder and OCD by limbic leucotomy is extremely sparse. Two studies have however reported post-operative improvement rates ranging from 38 per cent (Kelly, 1980), to 78 per cent in a depressed sample of 9 patients at 16 month follow-up (Mitchell-Heggs, Kelly & Richardson, 1976). Improvement rates of between 38 per cent (Hay et al, 1993) and 89 per cent (Mitchell-Heggs et al, 1976) have also been noted with regard to OCD patients treated by limbic leucotomy.

1.4.5 (e) Additional Comparative Efficacy Studies

Despite the slight fluctuation in procedural rates of improvement across different diagnostic categories, as noted in the former research, further studies have however demonstrated little difference between the operative procedures studied. Vasko & Kullberg (1979) investigated cognitive change following capsulotomy and cingulotomy and reported a higher incidence of deterioration in verbal memory with the former procedure, and in spatial tasks with the latter procedure. These impairments were however noted to have dissipated at longer term follow-up. A small number of studies which have investigated the comparative outcome of other neurosurgical procedures in treating OCD have also been published. Based on both therapist and patient ratings of the post-surgical change in obsessions, compulsions, anxiety and depression symptoms, Cosyns and colleagues reported significantly improved results at follow-up in those who had undergone subcaudate tractotomy, in comparison to the progressive leucocoagulation group (Cosyns et al, 1994). A subsequent study has also reported on the greatly improved clinical outcome of 16

patients with refractory OCD who had previously been treated by ventromedial leucotomy (Irle et al, 1998). The patient group was subdivided according to the exact lesion site targeted, but despite this the authors did not find significantly different effects

Summary

Given the clinical, ethical and methodological problems inherent in conducting research within the field of psychosurgery, a prospective randomised controlled trial has been outwith the realms of possibility to date. In the absence of such evidence, answers to important questions regarding the efficacy of the contemporary NMD procedures have typically had to rely on case series reports. Despite a 60 year history of such research there are still considerable methodological shortcomings within the published evidence base which limit any conclusions that may be drawn. As such, definitive certainty regarding the effectiveness of NMD procedures remains elusive; however, the available evidence does provide a relatively consistent approximation of the outcome following such operations. Evidence from a handful of controlled studies does appear to support the positive effect of such operative procedures, across a range of diagnostic conditions. Evidence drawn from consolidated reviews of outcome studies suggests a significant improvement rate of approximately 50 per cent in patients with depressive disorder, and OCD. Research reporting outcome on a relatively comparable 5-point outcome scale indicates significant improvement in one-third of patients with depressive illness, and OCD, with a further 20-30 per cent displaying only minor symptoms. There is at present

no significant evidence to suggest the significantly increased efficacy of any one procedure over another.

1.5 NMD - Adverse Effects

Despite low levels of reporting negative results following the pioneering psychosurgery operations, there were undoubtedly significant associated adverse effects. Freeman & Watts in 1942 acknowledged that patients often developed epileptic seizures, reduced attention, confusion, apathy, and changes in personality and appropriate social behaviour. Difficulties also frequently arose through complications with the non-sterile approach used, instrument breakage, and fatal haemorrhaging (Feldman & Goodrich, 2001). The operative mortality rate of such early procedures was approximately 4 per cent (Smith, 1977). Following considerable refinements in technique and improved target selection, several of the earlier surgical complications have now been eliminated. In practice today, there are considerably fewer serious adverse effects associated with the contemporary NMD procedures.

1.5.1 Physiological Effects

In common with other procedures which require intracranial surgery, there are general operative risks such as infection, haemorrhage, post-operative epilepsy, and confusional states, which may potentially raise complications. Despite this, the mortality rate for modern NMD procedures remains extremely low, and is comparable with results from other stereotactic neurosurgical procedures (Kiloh, 1983; Mindus & Meyerson, 1995). In a review of 854 operations, Kiloh and

colleagues reported a combined operative mortality rate of 0.1 per cent (Kiloh et al, 1988). There have been no reported deaths following anterior capsulotomy, cingulotomy, or limbic leucotomy (Ballantine et al, 1987; Cosgrove & Rauch, 1995; Mindus, 1993; Mitchell-Heggs et al, 1976), and only one death from a total of over 1300 patients treated by subcaudate tractotomy (Malhi et al, 1997). Hemiplegia has been noted in 0.03 per cent of cases following anterior cingulotomy (Ballantine et al, 1987; Marino & Cosgrove, 1997), with no such reports regarding the other common procedures. One case of cerebral haemorrhage following subcaudate tractotomy has been reported (Bridges et al, 1994); and 4 cases following anterior capsulotomy (Mindus, Edman & Andreewitch, 1999).

Chronic epilepsy was estimated in an earlier review to affect an overall rate of 0.4 per cent of patients following NMD (Kiloh et al, 1988). Including more recent data, the differential rate across procedures is now slightly higher; however, such seizures are generally noted to respond well to anti-convulsant therapy. Estimates suggest a prevalence rate of post-operative epilepsy in between 1 per cent and 2 per cent of individuals treated by subcaudate tractotomy (Fenton, 1998; Poynton et al, 1988) and anterior capsulotomy (Fenton, 1998); between 1 per cent and 9 per cent following anterior cingulotomy (Ballantine et al, 1987; Jenike et al, 1991); with no report of post-operative seizures following limbic leucotomy (Mitchell-Heggs et al, 1976), although it must be noted that anti-convulsants were routinely prescribed following surgery in the latter study.

The most commonly reported side-effects for all four procedures in the acute post-operative period include headaches, lethargy and, in a small minority of cases, confusion and disorientation, all of which are reported to resolve in the days and weeks following surgery (Bingley et al, 1977; Bridges et al, 1994; Jenike, 1998; Kelly, 1980; Meyerson & Mindus, 1988). It has been suggested that the latter disorientation and confusion may be related to post-operative oedema (Bridges et al, 1994; Hodgkiss et al, 1995; Mindus & Jenike, 1992; O'Doherty & Bridges, 1998). Clinically significant weight gain has also been reported following NMD procedures, in particular with regard to treatment by anterior capsulotomy and subcaudate tractotomy (Bridges et al, 1994; Herner, 1961; Mindus et al, 1994a). It remains unclear however as to whether this is a unique effect of specific procedures, or whether this effect is more widespread, but under-reported (Bingley et al, 1977; Mindus, 1993).

1.5.2 Personality Effects

Given that the functional targets for NMD procedures involve the interconnecting pathways between the frontal lobes and the limbic structures, an important issue in the evaluation of outcome is that regarding the potentially adverse effects such surgery may have on frontal lobe functioning and personality. Again, methodological issues confound the conclusions which may be drawn in this area of research. Varying measures of assessment with different definitions of personality have typically been employed with different diagnostic groups, across different surgical procedures. However, an approximation of opinion can be achieved through

reports from available outcome studies, and from a handful of studies specifically designed to measure this construct.

A review of a large series of NMD procedures, including a total of 854 patients, suggested that 'marked' personality change occurred in 0.4 per cent of patients who underwent stereotactic procedures, with 'mild' personality change noted in 3 per cent (Kiloh et al, 1988). Individual studies which have reported on each of the stereotactic NMD procedures have produced mixed results.

For each of the contemporary NMD procedures, there exists at least one study which has included assessment of personality traits (e.g. Eysenck Personality Inventory, Eysenck & Eysenck, 1964; and Minnesota Multiphasic Personality Inventory, Morey, Waugh & Blashfield, 1985), and reported negative changes in the post-operative period. For example, in the case of anterior capsulotomy minor changes were noted by Herner in 1961, and subsequently by Kullberg in 1977. The latter study reported the presence of increased disinhibition, emotional shallowness and loss of initiative following capsulotomy; however, these conclusions are limited by the subjectivity associated with the non-standardised nature of the assessments used. An outcome study investigating the effects of anterior cingulotomy also reported personality change in 11 per cent of the case series studied (Vilkki, 1977). Similar results were reported following subcaudate tractotomy (Goktepe et al, 1975; Strom-Olsen & Carlisle, 1971). The former study noted change in almost 7 per cent of patients, and the latter group reported 'moderate and lasting sequelae' in 2.6 per cent of their series, and 'minor & trivial frontal lobe symptoms' in 11 per cent.

However in contrast, there have also been a number of studies which have reported the lack of any negative personality change, following anterior capsulotomy (Bingley et al, 1977; Lopez-Ibor & Burzaco, 1972; Mindus, Nyman, Rosenquist, Rydin & Meyerson, 1988; Rylander, 1979); limbic leucotomy (Kelly, 1980); anterior cingulotomy (Long, Puschel & Hunter, 1978); and subcaudate tractotomy (Bridges et al, 1994). Recent prospective studies have employed more detailed assessment measures, specifically designed to address the issue of change in personality and frontal lobe function. Such studies have similarly failed to demonstrate any significant adverse personality change, at follow-up periods ranging from 1 year to 8 years (Mindus & Nyman, 1991; Mindus et al, 1999; Sachdev & Hay, 1995). The latter studies reported a gradual normalisation of personality features over time. This recent research provides further evidence to support the assertion that personality change does not occur as a consequence of NMD procedures per se.

Concerns do however continue to be raised regarding the long-term consequences of NMD on personality. The most recent study to report on the outcome of anterior capsulotomy in anxiety disorders highlighted the finding that 27 per cent of the patient group displayed adverse symptoms indicative of frontal lobe dysfunction (Ruck et al, 2003). These symptoms were measured on a rating scale specifically designed by the authors to measure frontal lobe function, and included measures of executive dysfunction, apathy, and disinhibition. Evidence of impaired 'theory of mind' following anterior capsulotomy has also been highlighted in a recent single case study (Happe, Gurjinder & Malhi, 2001). This raises the potential that more

specific deficits, for example, in the ability for social insight, may be adversely affected following such procedures.

1.5.3 Neuropsychological Effects

As is the case with other areas of outcome research in the field of NMD, there is a dearth of published literature investigating the neuropsychological effects of such ablative procedures. Many of the methodological criticisms levied at the general outcome literature can also be applied to the evidence base which has attempted to measure cognitive outcome. Neuropsychological research on NMD has typically included investigation of three main areas: (1) Comparisons between pre- and post-operative measures; (2) Comparisons between NMD patients and a normative sample; and (3) Comparisons between NMD patients and a control sample (Joschko, 1986). Evidence suggests the possibility of differential neuropsychological outcome with regard to general cognitive functioning and executive functioning. As such, these broad areas of functioning will now be addressed in turn.

1.5.3 (a) General Cognitive Function

Early investigation into the neuropsychological performance of NMD patients was typically limited to general measures of global intelligence, for example, the Wechsler Adult Intelligence Scale (Wechsler, 1981). More recent research has attempted to redress this issue by widening the scope of the neuropsychological assessment to include a more comprehensive investigation of additional cognitive functions. Despite the previously discussed methodological limitations, a consistency of opinion exists to suggest that there is no substantial evidence to

support a deterioration in general intellectual functioning following the modern stereotactic procedures, with the majority of studies highlighting the stability or improvement of general cognitive ability, for example: anterior capsulotomy (Bingley et al, 1977; Lopez-Ibor & Lopez-Ibor, 1977; Rylander, 1979; Vasko & Kullberg, 1979); anterior cingulotomy (Bailey, Dowling & Davies, 1977; Ballantine et al, 1967; Brown & Lighthill, 1968; Martin et al, 1977; Meyer, McElhaney, Martin & McGraw, 1973); stereotactic subcaudate tractotomy (Broseta, Barcia-Salorio, Roldan & Barbera, 1979); limbic leucotomy (Kelly, 1980; Mitchell-Heggs et al, 1976); and mixed operative groups (Cosyns et al, 1994; Herner, 1961; Vasko & Kullberg, 1979). There also exists a small evidence base of more recent research which was designed specifically to investigate the neuropsychological sequelae resulting from the contemporary surgical procedures, several of which have been conducted prospectively.

Recent research on the anterior capsulotomy procedure has highlighted the overall stability of general intellectual functioning following such surgery. In 1995, Nyman and Mindus investigated the neuropsychological performance of 10 individuals, five of whom had a primary diagnosis of OCD, and five with other anxiety disorders, both pre-operatively and at one year follow-up. The authors reported that post-capsulotomy performance across a range of general neuropsychological measures remained intact. Results of this study must be interpreted with caution, however, due to the small number of individuals involved.

Further research by Nyman and colleagues made similar claims regarding the stability of neuropsychological performance after capsulotomy (Nyman et al, 2001). This study is however subject to greater methodological flaws. The authors set out to assess the post-operative performance of 21 patients who had been treated with capsulotomy for OCD between 1978 and 1990. However, only 5 of the patients had been assessed with the same neuropsychological battery pre-operatively. Therefore, in order to make a comparison, the authors included the pre-operative results of 8 consecutive candidates for capsulotomy tested between 1993 and 1997. Results demonstrated that patients treated with capsulotomy performed between the lower end of the normal ability range to the mild impairment range, at post-operative follow-up. Subsequently, the authors concluded that when compared to the pre-operative performance of the smaller group who were awaiting surgery, there were no significant differences in performance found.

A recent report on the neuropsychological outcome following anterior capsulotomy on a series of patients with non-obsessional anxiety disorders, also noted that on a subtest which provides an estimate of pre-morbid intellectual ability, such individuals performed within the average range (Ruck et al, 2003).

Similar results were reported on early research which examined the neuropsychological performance of patients having undergone stereotactic anterior cingulotomy, using a range of assessment measures (Corkin et al, 1979; Long et al, 1978). Through pre- and post-operative assessment, results from the former study demonstrated no significant change across measures of general ability and memory

performance, in a mixed diagnostic group of 19 patients. The latter study reported on the neuropsychological performance of a series of patients with intractable pain and psychiatric disorder. The authors concluded that there was no evidence of any long-term impairment in cognitive function, as measured pre- and post-operatively by a battery of cognitive, sensory and motor tests. Until recently these have remained the only studies to have investigated neuropsychological outcome following anterior cingulotomy. However, a recent prospective study on 14 patients with refractory OCD has similarly demonstrated no evidence to support impairment on general measures of cognitive functioning when assessed at twelve month follow-up (Kim et al, 2003).

With regard to subcaudate tractotomy, a prospective study conducted on a series of 23 patients of mixed diagnoses examined neuropsychological performance across three occasions: pre-operatively; at the immediate post-operative stage; and at six months follow-up (Kartsounis et al, 1991). A variety of tests were used to assess premorbid intelligence, general ability, memory, attention and processing speed. The results demonstrated that general intellectual abilities remained stable following a period of six months. No significant deterioration was noted across any of the other tests used, with the exception of reduced performance in visual and verbal recognition memory and a notable increase in the tendency to confabulate on recall tasks at the immediate post-operative stage. The authors suggest that this impairment, which returned to pre-operative levels at follow-up, may be the result of transient dysfunction of the frontal lobes subsequent to acute post-operative oedema. With regard to the actual level of functioning observed, the authors highlighted a pre-

operative 10 point discrepancy between the NART (Nelson, 1982) and the WAIS full scale IQ score (Wechsler, 1981), which remained unchanged at follow-up. They concluded that such a discrepancy may indicate a mild degree of under-functioning amongst this severely ill group.

A retrospective German study conducted by Irle and colleagues reported results of a long term follow up of 16 patients who had undergone ventromedial frontal leukotomy for refractory OCD during the 1970's (Irle et al, 1998). This group was further divided into 3 groups depending on the lesion sites. They were compared to a smaller group of 7 patients who had not undergone surgery, but who also experienced refractory OCD. General neuropsychological assessment undertaken in 1992, demonstrated no significant difference between the 4 groups on full scale IQ or overall memory functioning. This study is however limited by the small numbers within each group and the lack of any intra-individual pre-operative comparison data. Similarly, Cummings and colleagues reported no significant differences in general intellectual ability or memory functioning, between a mixed-operative group of 17 OCD patients, the majority of whom underwent limbic leucotomy, and a non-surgical control group of 17 OCD patients (Cumming et al, 1995).

Summary

There exists within the literature a general concensus which suggests that significant loss of ability on a range of measures assessing general cognitive functioning is extremely rare with regard to the modern stereotactic procedures. Indeed, several follow up reports document slight improvement across a range of general cognitive

abilities. There also appears to be consistency amongst the evidence to suggest that NMD patients typically perform within the average to below average range on such neuropsychological measures when compared to a normative sample.

1.5.3 (b) Executive Function

Despite the seemingly unchanged general intellectual performance of individuals who have undergone NMD, this does not exclude the possibility that with more precise testing, impairment may be revealed on measures which specifically assess frontal lobe functioning. As the targets for neurosurgical intervention involve the interconnecting regions and pathways between the frontal lobes and the limbic structures, the procedures may be expected to affect the frontal area, which is known to be involved in higher executive functions (Lezak, 1995). As previously discussed, recent neuropsychological and neurophysiological research have also implicated the frontal regions of the brain, in studies conducted on individuals with depression and OCD.

One of the most widely acknowledged adverse effects reported across the various types of neurosurgical procedure is that described as ‘frontal lobe syndrome’. Evidence exists to suggest that whilst patients with frontal lobe lesions may perform relatively well on tests of general ability, impairment may be noted on more subtle tests designed specifically to assess executive function (Stuss & Benson, 1986). This ultimately raises the question of whether there may be other more subtle cognitive consequences which must be endured in return for any symptom alleviation gained from these neurosurgical procedures.

To date there have been very few published accounts that have focussed specifically on the neuropsychological outcome of the modern stereotactic procedures, and an even further reduced group that have included tests which are considered sensitive to frontal lobe functioning. It is only with relatively recent advances in the development of neuropsychological measures designed to assess the consequences of damage to the frontal region of the brain, that such 'executive' functions have become more quantifiable. However, the small evidence base which is available does provide some initial insight into this particular area of cognitive functioning at follow-up.

In a study investigating neuropsychological performance following anterior capsulotomy, Nyman and Mindus (1995) reported deterioration in half of their patient group (n=5) on a test of executive function, with a significantly lower number of categories completed and a higher rate of perseverative responses at follow-up, in comparison to the remaining patients. No significant difference was found in neuropsychological performance between the diagnostic groups.

A later study by Nyman and colleagues also reported post-operative executive dysfunction in a subgroup of 12 patients with OCD, following treatment with anterior capsulotomy (Nyman et al, 2001). Again this was noted through the lower number of categories completed on a recognised test of executive function. The authors however also state a positive correlation between the time elapsed after surgery and the number of categories completed, which they propose as evidence for

the restoration of this particular aspect of executive function and the transient nature of such initial impairment.

The most recent capsulotomy study reported the long-term neuropsychological performance in 17 patients with non-obsessional anxiety disorders (Ruck et al, 2003). A significantly lower than average performance was reported at one year follow-up on subtests which had been included with the aim of measuring executive function. Despite these results, the authors suggest that it may not be true to suggest that such impairment in executive function is a direct result of the surgical procedure. They refer to their previous study (Nyman et al, 2001) in which a group of OCD patients undergoing assessment for capsulotomy were shown to perform within the lower end of average or impaired range prior to surgery. Given that pre-operative measures of executive function were not conducted in this study, any conclusions regarding these issues remain limited. This study was also conducted on a diagnostic group who are not considered to be an appropriate indication for the use of NMD in the UK.

Long and colleagues investigated the neuropsychological effects of anterior cingulotomy in a group of 19 patients who were examined both pre- and post-operatively (Long et al, 1978). The authors concluded that such surgical intervention produces no significant decline in intellectual, memory, or higher cortical functions. However, with the exception of the Word Fluency subtest, which provides an estimate of executive functioning and in which a non-significant decline in scores was noted over time, the test battery employed in this early study did not appear to include many other specific neuropsychological measures of executive function.

Instead, a clinical assessment tool was used to evaluate changes in personality functioning before and after the surgical procedure, with which the authors themselves highlighted significant limitations.

A further study which examined the neuropsychological effects of anterior cingulotomy was that conducted by Corkin and colleagues (1979). The minority of subtests which demonstrated significant change in this study included a non-verbal fluency test and a complex figure test, both of which are purported to be sensitive to frontal lobe dysfunction (Lezak, 1995). Results indicated a significant difference on both subtests between the performance of those patients under and over 30 years of age. On the former test, the authors reported evidence demonstrating a lack of post-operative gain in the over-30 age group; and on the latter subtest, a significant deterioration in copy performance was noted in the same age group after surgery.

Since then, further research has produced evidence to suggest that there may be more subtle effects following cingulotomy which have previously gone unrecognised. A recent single case study of an individual who had undergone a bilateral anterior cingulotomy, used tests of visual cognition and attention to examine the hypothesis that the anterior cingulate cortex is an important part of an executive control system (Ochsner, Kosslyn, Cosgrove, Cassem, Price, Nierenberg et al, 2001). Results highlighted post-operative impairment on a variety of subtests which were demanding of such controlled processing, in the context of a normal pre-operative performance. The single case nature of this study does however limit the generalisability of its conclusions.

The most recent prospective research to compare the pre- and post-operative performance of 14 OCD patients following cingulotomy has reported no significant impairment on measures of executive function at twelve month follow-up (Kim et al, 2003). In contrast, the authors reported improvement on several subtests, through the reduction in the number of perseverative errors made.

In 1991, Kartsounis and colleagues were the first research group to conduct a prospective study of neuropsychological outcome which included measures designed to assess executive function abilities, in patients undergoing stereotactic subcaudate tractotomy. In this series, 23 patients of mixed diagnoses were assessed across three occasions: pre-operatively; at two weeks post-operatively; and at approximately 6 months follow-up. A range of neuropsychological tests were used, including six subtests proposed by the authors as being specific in their assessment of frontal lobe function. Results highlighted significant changes in executive functioning at the time of acute post-operative follow-up. In particular, a significant reduction in the number of words generated on a verbal fluency test was noted, as well as a significant reduction in the number of categories achieved on a modified card sorting test, and a higher number of errors and perseveration. This deterioration was noted in the context of the maintenance of general ability performance.

Further examination revealed that the former results returned to their pre-operative level at the 6 month follow-up assessment. The authors suggested that the deterioration in performance on tests of executive function, noted only during the acute post-operative phase, may in fact have resulted from transient oedema in the

frontal lobes, as opposed to a more permanent impairment resulting from actual tissue destruction. The increase in the number of confabulation responses which was also noted at post-operative memory recall was similarly suggested to be associated with the lack of ability to self-monitor and correct, an important aspect of executive functioning, rather than memory impairment per se.

Executive function in 17 patients with refractory OCD following mixed-operative procedures was compared to that of a matched control group of 17 patients with refractory OCD, who had not received any surgical procedure (Cumming et al, 1995). Results at follow-up highlighted the significantly poorer performance of the surgery group on a test of executive function in comparison to the control group, which the authors suggest may reflect the impact of frontal lobe lesions on higher executive functions. They do however also conclude that although the two groups did not differ in measured symptom severity, they estimate that the surgical group would have had more severe illness pre-operatively. They therefore deduce from this that the impairment noted on the test of executive function may actually be a result of their increased illness severity. Given that this study was not conducted longitudinally, the conclusions which may be drawn from this study are limited.

A further study examining neuropsychological function following ventromedial frontal leukotomy of varying lesion sites (Irle et al, 1998), reported a below average performance in all patients on a measure of executive function. Again, conclusions from this study are limited by the lack of comparative pre-operative neuropsychological data.

Summary

The current evidence base outlining the impact of NMD procedures on frontal functioning is both small and varied in its conclusions. Although transient impairment on specific measures of executive functioning has been reported, the absence of many longitudinal studies effectively limits any conclusions which may be drawn regarding the long term persistence of such deficits.

1.6 Present Study

1.6.1 Aims

The principle aim of the present study was to investigate the neuropsychological outcome following neurosurgery for mental disorder. In light of previous research, the specific aims were designed to elucidate the impact of such neurosurgical procedures on aspects of both general cognitive functioning, and executive functioning. In order to address the stated aims, the pre- and post-operative neuropsychological performance of an entire population of consecutive surgical candidates at a national centre for the provision of NMD, was explored. Following examination of the final data set, the general aims were refined to reflect the study of the neuropsychological impact of Anterior Capsulotomy, in the largest homogenous group of individuals, who had a primary diagnosis of intractable major depressive disorder.

1.6.2 Hypotheses

The specific hypotheses under investigation in the present study were as follows:

- **Hypothesis A:** Anterior capsulotomy will have no adverse effect on post-operative neuropsychological measures of general cognitive function.
- **Hypothesis B:** Anterior capsulotomy will have an adverse effect on post-operative neuropsychological measures of executive function.

CHAPTER 2 – METHOD

CHAPTER 2 - METHOD

2.1 Design

A repeated-measures design was used to investigate the neuropsychological performance of individuals who had undergone neurosurgery for the treatment of mental disorder. Within-subjects comparisons were made between individuals' pre- and post-operative performance on a range of clinical and computerised cognitive assessments.

In light of the practical and ethical issues associated with the inclusion of a suitable non-surgical, or sham control group in NMD research, a study of intra-individual design which examines the pre- and post-operative status of individuals who effectively act as their own controls, is considered to be the best alternative approach (Binder & Iskandar, 2000; Mindus & Jenike, 1992).

2.2 Ethical Approval

The present study was conducted with full ethical approval from the Tayside Committee on Medical Research Ethics (see Appendix).

2.3 Participants

The participants included in the present study comprised the entire sample of 28 consecutive patients who were treated by neurosurgery for mental disorder in the period between 1990 and 2003, at Ninewells Hospital, Dundee. The mean age of the overall group was 42.3 years, with a range of 30 to 64 years. The gender distribution

within the overall group was 21 female, and 7 male. The frequency of patients within each diagnostic category is displayed in Table 1.

Table 1. Frequency of Participants by Diagnostic Category (Entire Group)

| Diagnostic Categories | Frequency | Percentage |
|---|------------------|-------------------|
| Major Depressive Disorder | 23 | 82.1% |
| Bipolar Affective Disorder | 1 | 3.6% |
| OCD | 1 | 3.6% |
| OCD & Bipolar Affective Disorder | 1 | 3.6% |
| OCD & Major Depressive Disorder | 2 | 7.1% |

Of the total 28 patients treated by neurosurgery for mental disorder, 25 received bilateral anterior capsulotomy, and 3 received bilateral anterior cingulotomy, as their first procedure. Of the 25 patients initially treated with anterior capsulotomy, 6 individuals subsequently proceeded to have bilateral anterior cingulotomy as a second procedure.

2.4 Background Information – General Assessment Process

Referrals to the Scottish NMD service are accepted from centres throughout the UK and Ireland. Each individual in the present study had previously undergone a similar assessment process prior to acceptance as a suitable candidate for ablative neurosurgery. This preliminary assessment established the diagnostic classification of the treatment-refractory mental disorder experienced, and the degree of functional impairment endured, as well as the adequacy of previous psychological and physical treatments. Information regarding the criteria employed by the Scottish service in the consideration of candidates for NMD, and the guidelines adopted in the

assessment of previous treatment adequacy, have been outlined elsewhere (Matthews & Eljamel, 2003). At the same stage, independent assessments had also been conducted by the Mental Welfare Commission for Scotland to confirm potential candidates' suitability for surgery and their capacity to provide sustained and informed consent. As such, each of the participants included in the present study had been considered by the multidisciplinary teams involved in their referring area, by the Mental Welfare Commission for Scotland, and by the Scottish centre, as having provided informed consent for the procedure.

Once accepted as a suitable candidate for NMD, an extended period of pre-operative assessment had been undertaken, from which contributions to the process were provided by a multidisciplinary team consisting of a Consultant Psychiatrist, Consultant Neurosurgeon, Consultant Clinical Neuropsychologist, Consultant Clinical Psychologist and Consultant Psychiatrist in Psychotherapy. This assessment included structural brain imaging, mental state examination, and psychometric measures of personality, symptom severity, quality of life, as well as clinical and automated neuropsychological assessment. Follow-up assessment to repeat many of the baseline measures had typically been conducted in the acute post-operative stage, prior to the patient's return to their referral area. For many individuals, these assessments had been further repeated at variable longer term stages, depending on the patient's willingness to return for assessment, and the geographical distance involved.

2.5 Background Information – Neuropsychological Assessment Process

The principal aim of the present study was to investigate neuropsychological outcome following neurosurgery for mental disorder through the retrospective examination of neuropsychological assessment data. As such, examination of the outcome of any additional assessment measures, as previously outlined, were not considered to be within the realms of the present study.

Each individual in the present study had previously undergone neuropsychological assessment which had been administered in two independent formats, involving both clinical and computerised assessment. In the pre-operative phase, clinical and computerised neuropsychological assessments were administered within two weeks, on average, prior to surgery (Clinical range=1-34 days, SD=9.01; Computerised range=2-69 days, SD=17.03). Subsequent post-operative assessments had been conducted at varying time points. Computerised assessment had been administered in the acute post-operative phase prior to discharge from the Scottish centre, within an average of two weeks following surgery (Range=2-34 days; SD=8.46). A smaller number of individuals had undergone repeated computerised assessment following a longer term period, an average of two and a half years following surgery (Range=12-46 months; SD=13.83). A separate clinical neuropsychological assessment had also been conducted following a longer term period, an average of one year following surgery (Range=7-15 months; SD=2.77).

2.6 Procedure

In spite of the routine collection of a significant amount of neuropsychological assessment data since the inception of the Scottish NMD programme, as previously outlined, none of the information had previously been collated or systematically recorded in a readily accessible manner. Therefore, in order to examine the neuropsychological outcome in the current patient cohort, the initial process involved the identification of each participant's medical, psychiatric, and clinical psychology case notes. This provided individual demographic information, as well as details regarding the type and number of neurosurgical procedures each participant had previously undergone. Following this, in accordance with advice from the Data Protection Officer of Tayside University Hospitals Trust, a clinical database was established.

Information regarding the clinical neuropsychological assessments was held within the clinical psychology case notes, and took the form of raw data. As the principal aim of these assessments had been to provide a clinical impression of each individual's neuropsychological profile, and not solely to provide research data, many of the individual subtests had not been scored, or recorded in the standardised manner. Therefore, prior to entering such information onto the database, standardised scoring techniques were applied on a test by test basis, where required.

Information regarding the computerised neuropsychological assessments was held within the Department of Psychiatry, and took the form of three lengthy computer printouts per assessment. Some of this information was held within the psychiatry

case notes, whilst the remainder was retained on the original computer on which the assessments had been conducted. As the number of individual assessments had never officially been documented, considerable effort was invested in identifying the total number of completed assessments, which were multiple in number for some individuals, and relating them in time proximity to each participant's neurosurgical procedures. From this, it was then possible to identify with adequate consistency the relevant assessments to be entered onto the database.

Computerised assessments administered between the period of 1999 and 2003 were conducted on a revised Microsoft Windows-compatible version of the computerised system which provided summary statistics for each independent test. In order to extract the same statistics from the original version of the computerised system, on which a large majority of the participants had been assessed, calculations were required to ensure the compatibility of data between the original and revised systems. Therefore, such calculations were also performed on a test by test basis where necessary, prior to entering such information onto the database.

2.7 Measures

As previously stated, neuropsychological performance data had been derived both pre- and post-operatively from two independent forms of assessment: (1) Clinical neuropsychological assessment; and (2) Computerised neuropsychological assessment.

2.7.1 Clinical Neuropsychological Assessment

For the purpose of the present study, information relating to clinical performance scores was collected from a comprehensive battery of neuropsychological tests which assessed a wide range of cognitive functions including premorbid intelligence, general intellectual ability, executive functioning, memory, attention, and information processing speed. With few exceptions, all clinical neuropsychological assessments had been administered by the same clinician. Under specific circumstances with several patients a clinical decision was made not to administer particular subtests. This judgement was indicated in cases where an individual had clearly disengaged with the testing process as a result of extreme distress, fatigue, agitation, irritability, or distractibility. On other occasions particular subtests were not pursued as a result of the patient's absolute refusal to participate further. The decision not to administer certain subtests under these extreme circumstances was therefore made on a clinical and ethical basis with the ultimate aim being to elicit the maximum level of performance possible from each individual, in order to obtain the most valid and reliable neuropsychological assessment. As a result, performance data was not available for every subtest in the clinical battery, for every patient. An overview of the measures employed is outlined below.

2.7.1 (a) National Adult Reading Test (NART), 2nd edition, (Nelson, 1982; Nelson & Willison, 1991)

This word reading test was specifically designed for use in estimating the premorbid intelligence level of adults suspected to be suffering from intellectual deterioration (Nelson, 1982). The test requires that the individual reads aloud a list of 50

phonetically 'irregular' words, which are placed in ascending order according to level of difficulty. Test administration and scoring were conducted in accordance with the test manual (Nelson, 1982). The total error score, and predicted WAIS-R full scale IQ score were used in the analysis for the present study. The validity of the NART as a measure of general intelligence in a clinical population has been confirmed, alongside well-established reliability, with interrater coefficients of between 0.96 and 0.98, and test-retest coefficients of 0.98 (Crawford, Parker, Stewart, Besson, & De Lacey, 1989a).

2.7.1 (b) Wechsler Adult Intelligence Scale – Revised, (WAIS-R), (Wechsler, 1981)

The WAIS-R was designed to measure the current level of intellectual ability in adults aged between 16 and 74 years. Selected subtests were employed in the present study, which included two verbal subtests (Arithmetic and Comprehension), and two performance subtests (Block Design and Digit Symbol). Test administration and scoring were conducted in accordance with the test manual (Wechsler, 1981). Individual subtest raw scores were used in the subsequent analysis. An established evidence base exists to support the validity and reliability of the WAIS-R and is discussed within the test manual (Wechsler, 1981). Average reliability coefficients for the subtests used in the present study were reported to be 0.84 for the subtests of Arithmetic and Comprehension, 0.87 for Block Design, and 0.82 for Digit Symbol (Wechsler, 1981).

2.7.1 (c) Wechsler Memory Scale – Revised, (WMS-R), (Wechsler, 1987)

The WMS-R was designed to measure the current level of memory functioning in adults aged between 16 and 74 years. For the purpose of the present study selected subtests were employed, including: Digit Span; Logical Memory (Immediate & Delayed Recall); Verbal Paired Associates (Immediate & Delayed Recall); and Visual Reproduction (Immediate & Delayed Recall). Test administration and scoring were conducted in accordance with the test manual (Wechsler, 1987). Individual subtest raw scores were used in the subsequent analysis. Again, an established evidence base exists to support the validity and reliability of the WMS-R and is discussed within the test manual (Wechsler, 1987). Average reliability coefficients for the subtests used in the present study were reported to be 0.88 for Digit Span; 0.74 and 0.75 for Logical Memory Immediate and Delayed, respectively; 0.60 and 0.41 for Verbal Paired Associates Immediate and Delayed, respectively; and 0.59 and 0.46 for Visual Reproduction Immediate and Delayed, respectively (Wechsler, 1987).

The use of raw WAIS-R and WMS-R scores in the present study was given careful consideration with regard to the potential effects of using raw scores, as opposed to scaled scores, in a longitudinal study of this nature. Individual's performance scores would naturally be expected to deteriorate with age, an issue which would typically be adjusted for in the standardisation process. In order to account for the potential effects of increasing age on post-operative performance in the present study, each case was investigated to determine whether the length of follow-up period had affected the age band within which each individual fell. With clinical assessments

having been administered an average of one year following surgery (Range=7-15 months; SD=2.77), investigations revealed that none of the individuals had moved out with their pre-operative age band at post-operative follow-up, thereby confirming the appropriateness of pre- and post-operative comparisons using raw scores in the present study.

2.7.1 (d) Rey Complex Figure Test, (RCFT), (Meyers & Meyers, 1995)

This test was designed as a measure of perceptual organisation, visuospatial constructional ability and visual memory, and is standardised for use in adults aged between 18 and 89 years. The three drawing trials, namely Copy, Immediate and Delayed Recall, which comprise this test, were administered and scored in accordance with the test manual (Meyers & Meyers, 1995). The test requires that the individual initially copies a complex figure on to a blank sheet of paper. Then, after a three minute delay the individual is asked to draw the figure from memory. Following a further 30 minutes delay, the individual is again asked to draw the figure from memory. In cases where individuals had difficulty completing the initial copy trial, clinical judgement was used to determine whether to proceed with the additional trials. As such, visual inspection of the data revealed that very few individuals completed the immediate trial ($n=1$) or the long delay trial ($n=2$). It was therefore decided to exclude the latter trials from the current analysis in view of the small numbers involved. As such, only the raw scores for the copy trial were included in the analysis of the present study. Evidence to support the reliability and validity of this test is discussed within the accompanying test manual (Meyers & Meyers, 1995).

2.7.1 (e) Verbal Fluency Test (Lezak, 1995)

Reduced fluency of speech has been associated with the presence of aphasia and with frontal lobe damage (Lezak, 1995). A wide variety of word fluency tests exist which typically measure the number of words generated within a given category or beginning with a designated letter, within a restricted time limit. Evidence suggests that such measures of word fluency have proven sensitive to the effects of damage to the brain (Lezak, 1995). The test used in the current study assessed the number of words produced in three one-minute trials, within the category of 'Animals', and words beginning with the letters 'S', and 'J'. Visual inspection of the data revealed that very few individuals had completed the 'J' category (n=2). In cases where individuals had substantial difficulty in completing the preceding 'S' trial, the following 'J' category was often not administered, according to clinical judgement. It was therefore decided to exclude this category from the current analysis in view of the small numbers involved. As such, the total number of words, excluding repetitions, for the former two individual trials, 'Animals' and 'S', was analysed in the present study.

2.7.1 (f) Trail Making Test (Halstead-Reitan Battery, Reitan & Wolfson, 1993)

The Trail Making Test provides a measure of complex visual tracking and motor speed. As such, it has been reported as being highly vulnerable to the effects of brain injury (Lezak, 1995). The test is administered in two parts. Part A requires that the individual draws lines to connect a series of numbered circles in ascending order. Part B requires the individual to connect a series of numbers and letters in ascending order, by alternating between the two. The time taken for completion of each task is

recorded, and was used in the analysis in the present study. Reliability coefficients have previously been reported as 0.78 for Part A, and 0.67 for Part B (Lezak, 1995).

2.7.1 (g) California Verbal Learning Test, (CVLT), (Delis, Kramer, Kaplan, & Ober, 1987)

The CVLT was designed to provide a measure of recall and recognition of word lists across a number of trials, and can be administered from adolescence through to adults of any age. The test begins by evaluating the individual's ability to recall a list of 16 words over five trials. This is followed by the presentation of an interference list of 16 words. Immediately after this, free recall, and cued recall relating to the first list are assessed. Following a twenty minute delay, free recall, cued recall, and recognition of the first list are assessed. Test administration and scoring were conducted in accordance with the test manual which also provides detailed information in support of the reliability and validity of the test (Delis et al, 1987). Visual inspection of the data revealed that only one individual in the current cohort of participants had completed this measure. Again, the reasons for non-completion in some cases included individual's inability to follow through with the test, and on other cases a clinical decision was made not to administer it. As such, it was decided to exclude this test from the analysis in light of the small number of individual scores available.

2.7.1 (h) The Stroop Neuropsychological Screening Test, (SNST), (Trenerry, Crosson, DeBoe, & Leber, 1989)

A number of variations on the Stroop test exist, with the general aim of providing a measure of concentration effectiveness. The SNST format involves two separate trials, one of which requires the individual to name the colour of words printed in ink of different colours, and the other which requires the naming of the printed colours. Test administration and scoring were conducted in accordance with the test manual, which also provides information regarding the reliability and validity of the test (Trenerry et al, 1989). The SNST is standardised on adults aged upwards of 18 years. Again, a substantial number of the participants had not completed this task, due either to task difficulty or the clinical decision to exclude the test in individual cases. As such, it was decided to exclude this test from the analysis in light of the small number of individual scores available (n=1).

2.7.2 Computerised Neuropsychological Assessment

The comprehensive Cambridge Neuropsychological Test Automated Battery (CANTAB) had been used to conduct the computerised assessment of participants in the present study (Sahakian & Owen, 1992). It is comprised of three main test batteries, each designed to assess a specific area of cognitive function, namely: (1) Attention; (2) Visual Memory; and (3) Working Memory and Planning, which includes measures of executive function. The test items are all non-verbal, and are presented in a standardised form through the use of a touch-sensitive computer screen. The ability to adjust the level of difficulty through the grading of tasks is proposed to preclude the ceiling and floor effects often noted in comparable

neuropsychological measures. Published results have documented the use of the CANTAB as a measurement tool in a wide range of clinical presentations including psychiatric disorders, neurosurgical cases, neuro-degenerative conditions and acquired disease, and have reported its sensitivity in the detection of subtle deficits (Fray, Robbins & Sahakian, 1996). For the purpose of the present study, a reduced selection of tests were included in the analysis, an overview of which is outlined below. These particular measures were chosen for their reliability in measuring aspects of either general cognitive functioning or executive functioning, and were therefore the most salient measures of interest in relation to the current hypotheses.

2.7.2 (a) Pattern Recognition Memory

This test provides a measure of visual pattern recognition memory. The individual is initially presented with a series of visual patterns in the centre of the computer screen. Following this, a series of pairs of patterns are displayed, with one novel pattern and one which will be familiar to the individual. The test therefore requires that the individual identifies the familiar pattern. The score recorded for the purpose of the present analysis was the number of correct responses, expressed as a percentage.

2.7.2 (b) Spatial Span

This test provides a measure of spatial memory span. The individual is initially presented with a number of white squares dispersed across the computer screen, two of which temporarily change colour. The test requires that the individual must then touch the squares in the order in which they previously changed colour. The number

of squares in the sequence increases from two through to nine. The score recorded for the purpose of the present analysis was the longest sequence successfully recalled by the participant.

2.7.2 (c) Delayed Matching to Sample (DMS)

This test provides a measure of the participants' ability to remember a target stimulus following different lengths of time delay between the presentation of the stimulus and the presentation of the response choices. The individual is initially presented with a sample pattern in the centre of the computer screen. They are subsequently shown four patterns, one of which is identical to the sample pattern, the others of which are variations on the sample. The test requires that the individual identify the pattern that matches the sample. The choice is made in four different conditions: (1) Simultaneous, where the sample pattern and choices are available to view at the same time; (2) Short delay, where a zero second delay ensues between the presentation of the sample pattern and choices; (3) Medium delay, following a four second delay; and (4) Long delay, following a twelve second delay. The scores recorded for the purpose of the present analysis were the number of occasions, expressed as a percentage, on which the individual selected the correct stimulus in the former four conditions, and on a fifth condition involving a combination of performance across each of the time delays.

2.7.2 (d) Intra/Extra-Dimensional Shift (IED)

This test provides a measure of ability to attend to specific attributes of presented stimuli, and to shift that attention when required. The individual is initially presented

with two simple colour-filled shapes. The individual must subsequently learn which shape is correct, through touching the screen. The computer indicates whether their response was correct or not, and the individual must use this feedback to develop and learn the relevant rules. Once the individual has effectively learnt the relevant rule by reaching criterion (i.e. 6 consecutive correct responses), the rule is reversed, and what was previously correct becomes incorrect and vice versa. The rule becomes increasingly more complex as the test progresses. As the test proceeds, two different types of attentional shift take place. The intra-dimensional shift involves the introduction of new examples of the stimulus, whilst the original dimension of shape remains constant. The extra-dimensional shift requires that the individual shifts attention to the previously irrelevant dimension, to discover which of the new stimuli are correct. The scores recorded for the purpose of the present analysis included: (1) the total number of stages completed; (2) the total number of errors made on the test, therefore providing a measure of the individual's efficiency in attempting the test; (3) the number of errors made prior to the extra-dimensional shift stage; (4) the number of errors made in the extra-dimensional shift stage; and (5) the total number of errors made, whilst adjusting for the number of stages not completed.

2.7.2 (e) Spatial Working Memory (SWM)

This test provides a measure of spatial working memory. The individual is initially presented with a number of coloured boxes on the computer screen which they must touch in turn, until a blue token is displayed inside one of the boxes. Once found, a blue token will never be placed in the same box again. The test therefore requires that the individual remembers the previous location of the token in order to avoid

error. Two types of error can be made on this test: (1) Between search error, in which the individual returns to a location in which a token was previously found; and (2) Within search error, in which the individual returns to the same empty box twice. The number of boxes, and tokens to be found increases with each level completed. The between search errors and total number of errors were recorded for the purpose of the analysis.

2.7.2 (f) Stockings of Cambridge (SOC)

This test provides a measure of an individual's planning ability. The individual is initially presented with two displays of what are described as coloured balls hanging in stockings or socks. The test requires that the individual must move the balls in the lower display to match the target display at the top of the screen. The individual is initially required to make only one move, which later increases to four moves as the test progresses. The individual is told the minimum number of moves required to achieve the target sequence and is encouraged to consider their solution prior to making a move. The time taken and the number of moves made are extracted as a measure of the individual's planning ability.

CHAPTER 3 – RESULTS

CHAPTER 3 – RESULTS

3.1 Participants

3.1.1 Group A: Anterior Capsulotomy

A total of 25 participants underwent treatment by anterior capsulotomy as their first neurosurgical procedure. The mean age of this group was 43 years (SD=9.6), with a range of 30 to 64 years. The gender distribution was 18 female, and 7 male. The frequency of patients within each diagnostic category is displayed in Table 2.

Table 2. Frequency of Participants by Diagnostic Category (Group A)

| Diagnostic Categories | Frequency | Percentage |
|----------------------------------|-----------|------------|
| Major Depressive Disorder | 20 | 80% |
| Bipolar Affective Disorder | 1 | 4% |
| OCD | 1 | 4% |
| OCD & Bipolar Affective Disorder | 1 | 4% |
| OCD & Major Depressive Disorder | 2 | 8% |

3.1.2 Exclusions from Overall Data Set

Three individuals were excluded from the entire data set, prior to statistical analysis. Individual 1 was excluded as they had suffered a significant vascular event following surgery, thereby confounding the neuropsychological results. Individual 2 was excluded as they had previously undergone a stereotactic subcaudate tractotomy at another hospital, for which there was no assessment information available. Individual 3 was excluded as they underwent a total of three separate anterior capsulotomy procedures, for which there was no available pre-operative assessment

information. Therefore, an overall total of 22 individuals were included for analysis in the present study.

3.1.3 Final Sample

Following the aforementioned exclusions from the data set, the final sample of individuals who had undergone neurosurgical treatment by anterior capsulotomy, on which exploratory and statistical analysis was conducted, is summarised in Table 3.

Table 3. Final Sample Demographics

| | Clinical Assessment | Computerised Assessment | |
|---------------------|-------------------------|--------------------------|-------------------------|
| | Pre & Long Term Post-op | Pre & Short Term Post-op | Pre & Long Term Post-Op |
| <i>Age</i> | | | |
| Mean | 42.95 | 42.95 | 42.44 |
| SD | 10.04 | 10.04 | 10.33 |
| Range | 30 – 64 | 30 – 64 | 30 – 61 |
| <i>Gender</i> | | | |
| Male | 6 | 6 | 4 |
| Female | 16 | 16 | 5 |
| <i>Diagnosis</i> | | | |
| Depressive Disorder | 17 | 17 | 5 |
| Bipolar Disorder | 1 | 1 | 1 |
| OCD | 1 | 1 | 1 |
| OCD & Depression | 1 | 1 | 1 |
| OCD & Bipolar | 2 | 2 | 1 |
| <i>Total</i> | 22 | 22 | 9 |

3.1.4 Sample Size

Successfully conducting both pre- and post-operative follow-up assessments in a sample of individuals of which the majority are tertiary referrals, is a widely acknowledged difficulty in the field of NMD research. Follow-up assessments with such individuals are often hampered by factors such as geographical distance, and in several cases, by patients’ understandable reluctance or unwillingness to return for further assessment when they consider themselves to be improved and to have

moved on in their lives. Therefore, despite every effort, it is inevitable that there are often a number of individuals for whom only one assessment, either pre- or post-operative, is available. This was noted to be the case with the present sample, and accounts for some of the difference observed between the total number of participants who received surgery, and the final number reported on each individual subtest.

Another contributing factor to this difference in numbers is that related to the severity of illness experienced amongst this very select population group. As a result, many of these individuals were unable to attempt, or to complete a variety of the individual subtests given. This was accounted for by the statistical package in use, SPSS-11.5 (SPSS, 2002), which effectively removed cases with missing values from the analysis on an individual test basis. In light of the fact that the current study employed a within-subjects repeated-measures design, variable sample sizes were therefore recorded across individual subtests for both computerised and clinical neuropsychological assessment data. The total number of participants who completed each subtest was therefore reported on a test-by-test basis.

3.1.5 Group B: Anterior Cingulotomy

A total of 3 patients underwent anterior cingulotomy as their first neurosurgical procedure. The mean age of this group was 35.7 years (SD=5.5), with a range of 30 to 41 years. All three patients were female, and had a primary diagnosis of major depressive disorder.

3.1.6 Group C: Multiple Procedures

Of the previous 25 anterior capsulotomy patients, 6 individuals subsequently proceeded to undergo treatment by anterior cingulotomy, as a second neurosurgical procedure. The mean age of this group was 39.8 years (SD=8.38), with a range of 30 to 51 years. The gender distribution within this group was 4 female, and 2 male. Five individuals had a primary diagnosis of major depressive disorder, and one had a dual diagnosis of OCD and major depressive disorder.

3.2 Results – Group A: Anterior Capsulotomy

3.2.1 Exploratory Data Analysis – Combined Diagnostic Group

In the case of both computerised and clinical neuropsychological assessment data, exploratory analysis was initially conducted to examine the nature of the entire data set. Given that the present study employed a within-subjects repeated-measures design, the issue of normality primarily reflected the mean ‘difference’ between the neuropsychological scores before and after treatment by anterior capsulotomy. Therefore, investigation regarding the distribution of such mean difference scores was initially conducted for the entire group of individuals who underwent this neurosurgical procedure, regardless of their diagnosis.

Exploratory data analysis revealed that the mean pre- and post-operative difference scores in the smaller diagnostic groups fell outwith the mean scores of the larger depressive disorder group on a small number of subtests, within both the computerised and clinical neuropsychological assessment data. Despite the small number of subtests affected, it was considered statistically inadvisable to combine

the diagnostic groups in further analysis, in light of the potentially confounding effect such cases may have exerted on the remaining data. As such, a decision was made to report the comparison of pre- and post-operative neuropsychological scores for the larger depressive disorder group first, followed by individual reports on each of the other individual diagnostic categories. As the number of individuals in diagnostic categories other than depressive disorder was so few, a between-subjects comparison was not statistically possible however, comments were made regarding the general trend of the data. This format was applied to both the computerised and clinical assessment data.

3.2.2 Exploratory Data Analysis – Individual Diagnostic Groups

Exploratory data analysis was subsequently conducted to investigate the nature of the data within each individual diagnostic group. As the number of individuals within each diagnostic category other than depressive disorder did not exceed two, this analysis primarily related to the depressive disorder category. The Kolmogorov-Smirnov test was initially conducted as a check against gross departures from normality. Further exploratory analysis revealed the presence of outliers on a small number of subtests. Given that so few subtest scores were found to notably depart from the mean, it was decided not to transform or remove these cases. This decision was supported by the clinicians involved in the original assessment process, who considered the latter performance scores to be a true reflection of each individual's ability at that time.

3.2.3 Statistical Analysis

Therefore, in the presence of very few outlying scores, it was decided to conduct formal statistical analysis with parametric tests; given that the Kolmogorov-Smirnov test had indicated no extreme departures from normality, and the within-subjects comparison groups contained equal sample sizes. It is also well-established that parametric tests are considered robust even under departures from underlying assumptions (Clark-Carter, 1997). As such, Paired Samples *t*-tests were employed across the data set. The small samples involved in some of the analysis must be borne in mind when drawing conclusions from these results, however in view of the former exploratory analysis, the *t*-test was still considered to be the most powerful measure of the present data set. Statistical computations were based on participant's raw scores, with the exception of the latency scores on the Stockings of Cambridge test, which were transformed into logarithms (base 10). All analyses were performed using SPSS 11.5 for Windows (SPSS, 2002).

3.2.4 Statistical Power

Prospective power calculations were not conducted in the design stage of the present study, in light of the fact that the current sample included the entire population of participants who had undergone neurosurgery for mental disorder at the Scottish centre since its inception in 1990. The most relevant use of the power calculation under these circumstances was therefore considered to be that conducted retrospectively, with the aim of providing an estimate of the power of the statistical tests employed within the present study, to detect an effect where present (Clark-Carter, 1997). Therefore, such calculations revealed that the sample size available

for participation in the present study would only enable detection of a relatively large effect size, using within-subjects' comparisons (Clark-Carter, 1997).

3.2.5 Background Information

In order to facilitate a clearer understanding of the forthcoming presentation of results, the time points at which neuropsychological assessments were conducted will be briefly summarised. Both computerised and clinical neuropsychological assessments were conducted within an average of two weeks prior to surgery. Computerised assessment was then repeated at two independent follow-up stages: (1) 'short term', denoting assessments conducted an average of two weeks post-operatively; and (2) 'long term', denoting assessments conducted an average of two and a half years post-operatively. Clinical assessment was repeated at one 'long term' follow-up stage, conducted an average of one year post-operatively. Clarification of the abbreviations used to represent subtest names within the forthcoming tables and figures is presented in Table 4 for the computerised assessments and, in Table 5 for the clinical assessments.

Table 4. Abbreviations of Subtest Names – Computerised Assessment

| Abbreviation Name | Subtest |
|-------------------|---|
| - Patt. Recog. | - Pattern Recognition Memory - % correct |
| - Span Length | - Spatial Span Length |
| - DMS-Simul. | - Delayed Matching to Sample - % correct - Simultaneous |
| - DMS-All | - Delayed Matching to Sample - % correct - All Delays |
| - DMS-Short | - Delayed Matching to Sample - % correct - Short Delay |
| - DMS-Med | - Delayed Matching to Sample - % correct - Medium Delay |
| - DMS-Long | - Delayed Matching to Sample - % correct - Long Delay |
| - SOCinitial | - Stockings of Cambridge – Mean Initial Thinking Time |
| - SOCsubs | - Stockings of Cambridge – Subsequent Thinking Time |
| - SOCprobs | - Stockings of Cambridge-Problems Solved Minimum Moves |
| - IED-stages | - Intra/Extra-Dimensional Shift – Stages Completed |
| - IED-total err | - Intra/Extra-Dimensional Shift – Total Errors |
| - IED-pre-ed | - Intra/Extra-Dimensional Shift – Pre-Extra Dim. Shift Errors |
| - IED-eds err | - Intra/Extra-Dimensional Shift – Extra Dim. Shift Errors |
| - IED-err.adj | - Intra/Extra-Dimensional Shift – Total Errors Adjusted |
| - SWM-bet.err. | - Spatial Working Memory – Between Search Errors |
| - SWM-tot.err. | - Spatial Working Memory – Total Errors |
| - SWM-4 box | - Spatial Working Memory – Between Search Errors - 4 boxes |
| - SWM-6 box | - Spatial Working Memory – Between Search Errors - 6 boxes |
| - SWM-8 box | - Spatial Working Memory – Between Search Errors - 8 boxes |

Table 5. Abbreviations of Subtest Names – Clinical Assessment

| Abbreviation Name | Subtest |
|-------------------|---|
| - Nart Error | - NART – Error Score |
| - Nart FSIQ | - NART – Predicted Full Scale IQ Score |
| - DigSpan-F | - WMS-R – Digit Span Forwards (digits recalled) |
| - DigSpan-B | - WMS-R – Digit Span Backwards (digits recalled) |
| - LogMemI | - WMS-R – Logical Memory – Immediate Recall |
| - LogMemD | - WMS-R – Logical Memory – Delayed Recall |
| - PairAss-I | - WMS-R – Verbal Paired Associates – Immediate Recall |
| - PairAss-D | - WMS-R – Verbal Paired Associates – Delayed Recall |
| - VisRepr-I | - WMS-R – Visual Reproduction – Immediate Recall |
| - VisRepr-D | - WMS-R – Visual Reproduction – Delayed Recall |
| - Arithmetic | - WAIS-R – Arithmetic |
| - Compreh. | - WAIS-R – Comprehension |
| - Block Des | - WAIS-R – Block Design |
| - DigSym | - WAIS-R – Digit Symbol |
| - Rey-Copy | - Rey Complex Figure Test – Copy Condition |
| - Trails A | - Trail Making Test – Trails ‘A’ Condition |
| - Trails B | - Trail Making Test – Trails ‘B’ Condition |
| - Fluency-A | - Verbal Fluency Test – ‘Animals’ Condition |
| - Fluency-S | - Verbal Fluency Test – ‘S’ Condition |

3.2.6 Hypothesis A – Results

- **Hypothesis A:** Anterior capsulotomy will have no adverse effect on post-operative neuropsychological measures of general cognitive function.

3.2.6 (a) Computerised Assessment – Short Term Follow-Up – Depressive Disorder

The following presentation of data represents the pre- and short term post-operative comparison of the computerised neuropsychological assessment of general cognitive function, regarding a total of 17 individuals with major depressive disorder, who underwent treatment by Anterior Capsulotomy. An overview of the pre- and short term post-operative mean scores, standard deviations, and statistical comparisons is displayed in Table 6.

Table 6. (Hyp. A) CANTAB – Short Term Follow-Up – Depressive Disorder

| General Cognitive Function Subtests | Pre-operative | | | Short Term Follow-Up | | | Paired Samples <i>t</i> -tests | | | Trend |
|--|---------------|-------|-------|----------------------|-------|-------|--------------------------------|----|----------|-------|
| | N | Mean | SD | N | Mean | SD | <i>t</i> | df | sig. | |
| <i>Pattern Recog. Memory</i> | 12 | 69.47 | 20.56 | 12 | 70.21 | 21.93 | 0.25 | 11 | 0.81 NS | + |
| <i>Spatial Span Length</i> | 13 | 4.46 | 1.56 | 13 | 4.15 | 1.68 | 0.84 | 12 | 0.42 NS | - |
| <i>Del. Matching to Sample</i> | | | | | | | | | | |
| Simultaneous Condition | 10 | 97.00 | 6.75 | 10 | 94.00 | 9.66 | 1.15 | 9 | 0.28 NS | - |
| All Delays | 10 | 62.00 | 29.32 | 10 | 50.67 | 23.77 | 2.52 | 9 | 0.03 SIG | - |
| Short Delay | 10 | 70.00 | 32.66 | 10 | 58.00 | 28.60 | 1.69 | 9 | 0.13 NS | - |
| Medium Delay | 10 | 64.00 | 29.52 | 10 | 56.00 | 25.47 | 2.45 | 9 | 0.04 SIG | - |
| Long Delay | 10 | 52.00 | 32.25 | 10 | 38.00 | 25.73 | 1.68 | 9 | 0.13 NS | - |

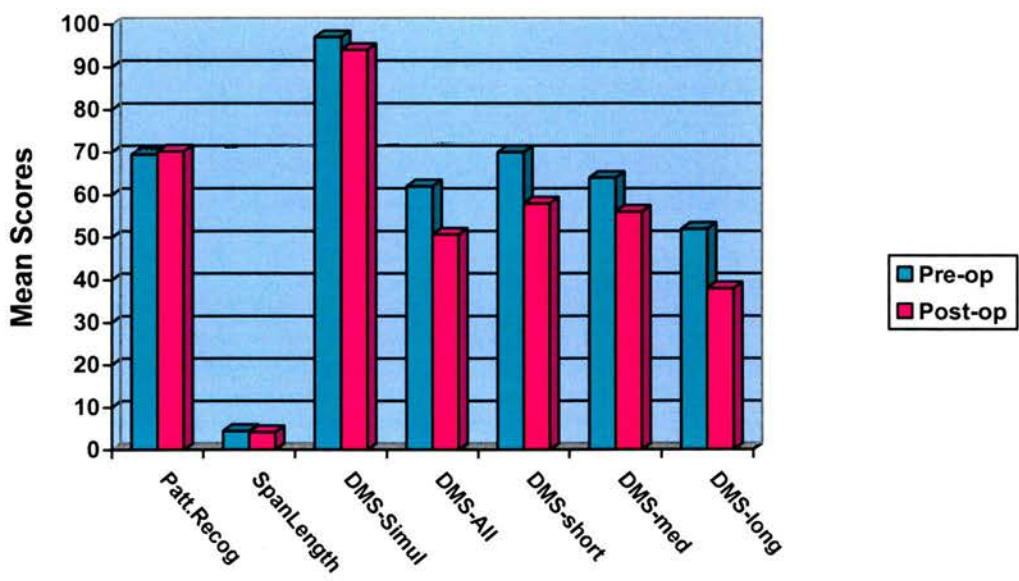
Note: NS = not significant ($p > 0.05$); **SIG** = significant ($p < 0.05$).

Note: **Trend** refers to the non-significant direction of improvement (+), or impairment (-).

3.2.6 (b) Summary of Results

Paired samples *t*-tests revealed that a statistically significant impairment, at the $p<0.05$ level, was noted on two subtests from the Delayed Matching to Sample test. Performance scores on the combined average of all delays demonstrated a statistically significant impairment at post-operative assessment [$t(9)=2.52$; $p<0.05$], as did scores at the medium delay condition [$t(9)=2.45$; $p<0.05$]. No other subtest measuring general cognitive function from the computerised neuropsychological assessment battery achieved statistical significance at this stage. Examination of the trend of change at short term follow-up revealed a pattern of non-significant impairment in performance with the exception of one subtest. Visual presentation of these scores is illustrated in Figure 3, with improvement in performance indicated by a post-operative increase in score, and impairment indicated by a decrease in score.

Figure 3. (Hyp. A) CANTAB – Pre & Short Term Comparison – Depressive Disorder



3.2.6 (c) Computerised Assessment – Short Term Follow-Up – Other Diagnostic Categories

The following presentation of data represents the pre- and short term post-operative comparison of the computerised neuropsychological assessment of general cognitive function, regarding a total of 5 individuals who also underwent anterior capsulotomy for the treatment of diagnoses other than depressive disorder. An overview of the pre- and short term post-operative follow-up scores for each of the individual diagnostic categories is displayed in Table 7. Visual inspection of this data revealed a similar pattern of results to that of the depressive disorder group. The minor fluctuation between pre- and post-operative scores appeared to reflect the presence of both improvement and impairment.

Table 7. (Hyp. A) CANTAB – Short Term Follow-Up – Other Diagnostic Categories

| General Cognitive Function Subtests | OCD (n=1) | | Bipolar Disorder (n=1) | | OCD & Bipolar (n=1) | | OCD & Depressive Disorder (n=2) | |
|--|--------------|-------------|---------------------------|-------------|------------------------|-------------|------------------------------------|-----------------|
| | Pre- Op | Post- Op | Pre- Op | Post- Op | Pre- Op | Post- Op | Mean Pre-Op | Mean Post-Op |
| <i>Pattern Recog. Memory</i> | 54.17 | 66.67 | 58.00 | 58.50 | 91.50 | 100.00 | 87.5 | 75.00 |
| <i>Spatial Span Length</i> | 3.00 | 3.00 | 4.00 | 3.00 | 6.00 | 5.00 | 5.00 | 5.50 |
| <i>Del. Matching to Sample</i> | | | | | | | | |
| Simultaneous Condition | 80.00 | 80.00 | 100.00 | 90.00 | 100.00 | 100.00 | 100.00 | 100.00 |
| All Delays | 43.33 | • | 33.33 | 56.67 | 86.67 | 80.00 | 83.33 | 81.67 |
| Short Delay | 30.00 | • | 40.00 | 60.00 | 90.00 | 100.00 | 100.00 | 80.00 |
| Medium Delay | 50.00 | • | 20.00 | 70.00 | 100.00 | 80.00 | 60.00 | 90.00 |
| Long Delay | 50.00 | • | 40.00 | 40.00 | 70.00 | 60.00 | 90.00 | 75.00 |

Note: (•) represents a missing data value.

3.2.6 (d) Computerised Assessment – Long Term Follow-Up – Depressive Disorder

The following presentation of data represents the pre- and long term post-operative comparison of the computerised neuropsychological assessment of general cognitive function, regarding a total of 5 individuals with major depressive disorder, who underwent treatment by Anterior Capsulotomy. An overview of the pre- and long term post-operative mean scores, standard deviations, and statistical comparisons is displayed in Table 8.

Table 8. (Hyp. A) CANTAB – Long Term Follow-Up – Depressive Disorder

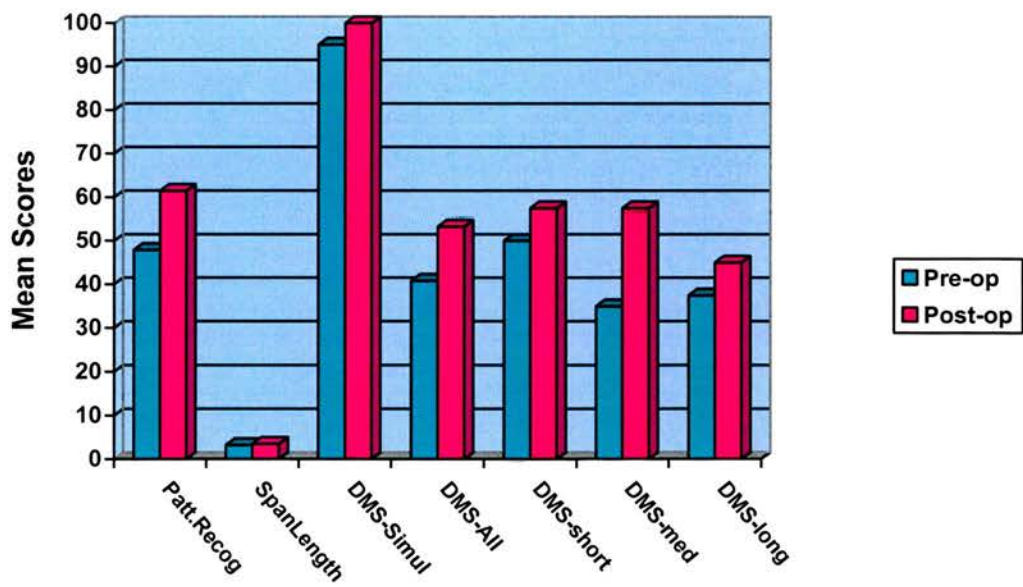
| General Cognitive Function Subtests | Pre-operative | | | Long Term Follow-Up | | | Paired Samples <i>t</i> -tests | | | | Trend |
|--|---------------|-------|-------|---------------------|--------|-------|-----------------------------------|----|------|-----|-------|
| | N | Mean | SD | N | Mean | SD | <i>t</i> | df | sig. | | |
| <i>Pattern Recog. Memory</i> | 4 | 47.91 | 15.29 | 4 | 61.46 | 12.90 | 2.34 | 3 | 0.10 | NS | + |
| <i>Spatial Span Length</i> | 4 | 3.25 | 1.26 | 4 | 3.50 | 1.29 | 1.00 | 3 | 0.39 | NS | + |
| <i>Del. Matching to Sample</i> | | | | | | | | | | | |
| Simultaneous Condition | 4 | 95.00 | 5.77 | 4 | 100.00 | 0.00 | 1.73 | 3 | 0.18 | NS | + |
| All Delays | 4 | 40.84 | 31.55 | 4 | 53.22 | 16.65 | 1.53 | 3 | 0.22 | NS | + |
| Short Delay | 4 | 50.00 | 42.43 | 4 | 57.50 | 28.72 | 0.52 | 3 | 0.64 | NS | + |
| Medium Delay | 4 | 35.00 | 20.82 | 4 | 57.50 | 26.30 | 4.70 | 3 | 0.02 | SIG | + |
| Long Delay | 4 | 37.50 | 33.04 | 4 | 45.00 | 12.91 | 0.55 | 3 | 0.62 | NS | + |

Note: NS = not significant ($p > 0.05$): **SIG** = significant ($p < 0.05$).
Note: **Trend** refers to the non-significant direction of improvement (+), or impairment (-).

3.2.6 (e) Summary of Results

Paired samples *t*-tests revealed that a statistically significant improvement, at the $p<0.05$ level, was demonstrated on the Delayed Matching to Sample subtest that measured the total percentage correct in the medium delay condition [$t(3)=4.70$; $p<0.05$]. No other subtest measuring general cognitive function from the computerised neuropsychological assessment battery achieved statistical significance at this stage. Examination of the trend of change at long-term follow-up revealed a pattern of non-significant improvement in performance across all of the subtests administered. Visual presentation of these scores is illustrated in Figure 4, with improvement in performance indicated by a post-operative increase in score, and impairment indicated by a decrease.

Figure 4. (Hyp. A) CANTAB – Pre & Long Term Comparison – Depressive Disorder



3.2.6 (f) Computerised Assessment – Long Term Follow-Up – Other Diagnostic Categories

The following presentation of data represents the pre- and long term post-operative comparison of the computerised neuropsychological assessment of general cognitive function, regarding a total of 4 individuals who also underwent anterior capsulotomy for the treatment of diagnoses other than depressive disorder. An overview of the pre- and long term post-operative follow-up scores for each of the individual diagnostic categories is displayed in Table 9. Visual inspection of this data revealed a similar pattern of results to that of the depressive disorder group. Minor fluctuation between the pre- and post-operative performance scores did occur across individuals and subtests however, on the majority of the measures such fluctuation reflected an improvement.

Table 9. (Hyp. A) CANTAB – Long Term Follow-Up – Other Diagnostic Categories

| General Cognitive Function Subtests | OCD (n=1) | | Bipolar Disorder (n=1) | | OCD & Bipolar (n=1) | | OCD & Depressive Disorder (n=1) | |
|--|--------------|-------------|---------------------------|-------------|------------------------|-------------|------------------------------------|-------------|
| | Pre- Op | Post- Op | Pre- Op | Post- Op | Pre- Op | Post- Op | Pre- Op | Post- Op |
| <i>Pattern Recog. Memory</i> | 54.17 | 75.00 | 58.00 | 58.33 | 91.50 | 100 | • | 79.17 |
| <i>Spatial Span Length</i> | 3 | 4 | 4 | 5 | 6 | 6 | • | 5 |
| <i>Del. Matching to Sample</i> | | | | | | | | |
| Simultaneous Condition | 80 | 100 | 100 | 100 | 100 | 100 | • | 100 |
| All Delays | 43.33 | 60 | 33.33 | 66.67 | 86.67 | 83.33 | • | 76.67 |
| Short Delay | 30 | 80 | 40 | 60 | 90 | 100 | • | 90 |
| Medium Delay | 50 | 60 | 20 | 100 | 100 | 90 | • | 70 |
| Long Delay | 50 | 40 | 40 | 40 | 70 | 60 | • | 70 |

Note: (•) represents a missing data value.

3.2.6 (g) Clinical Assessment – Long Term Follow-Up - Depressive Disorder

The following presentation of data represents the pre- and long term post-operative comparison of the clinical neuropsychological assessment of general cognitive function, regarding a total of 17 individuals with major depressive disorder, who underwent treatment by Anterior Capsulotomy. An overview of the pre- and long term post-operative mean scores, standard deviations, and statistical comparisons is displayed in Table 10.

Table 10. (Hyp. A) Clinical – Long Term Follow-Up – Depressive Disorder

| General Cognitive Function Subtests | Pre-operative | | | Post-operative | | | Paired Samples <i>t</i> -tests | | | Trend | |
|--|---------------|--------|-------|----------------|--------|-------|--------------------------------|----|------|-------|---|
| | N | Mean | SD | N | Mean | SD | <i>t</i> | df | sig. | | |
| <i>NART</i> | | | | | | | | | | | |
| Error | 4 | 12.00 | 8.04 | 4 | 7.25 | 5.19 | 1.19 | 3 | 0.32 | NS | + |
| FSIQ | 4 | 116.00 | 10.03 | 4 | 121.50 | 6.40 | 1.16 | 3 | 0.33 | NS | + |
| <i>WMS-R</i> | | | | | | | | | | | |
| Digit Span-Forward | 11 | 6.09 | 1.45 | 11 | 6.18 | 1.33 | 0.21 | 10 | 0.84 | NS | + |
| Digit Span-Backward | 11 | 3.73 | 1.79 | 11 | 4.18 | 0.98 | 1.05 | 10 | 0.32 | NS | + |
| Log. Memory-Imm. | 11 | 13.00 | 6.69 | 11 | 17.45 | 7.89 | 1.97 | 10 | 0.08 | NS | + |
| Log. Memory-Del. | 10 | 6.50 | 5.70 | 10 | 11.80 | 8.04 | 1.99 | 9 | 0.08 | NS | + |
| Paired Assoc.-Imm. | 7 | 16.00 | 4.62 | 7 | 17.00 | 4.16 | 0.41 | 6 | 0.70 | NS | + |
| Paired Assoc.-Del. | 6 | 5.33 | 1.51 | 6 | 6.00 | 2.10 | 0.76 | 5 | 0.48 | NS | + |
| Visual Reprod.-Imm. | 8 | 25.88 | 8.89 | 8 | 31.38 | 2.97 | 2.07 | 7 | 0.08 | NS | + |
| Visual Reprod.-Del. | 7 | 12.14 | 12.63 | 7 | 13.71 | 8.34 | 0.27 | 6 | 0.79 | NS | + |
| <i>WAIS-R</i> | | | | | | | | | | | |
| Arithmetic | 8 | 8.25 | 3.24 | 8 | 8.63 | 3.25 | 0.30 | 7 | 0.77 | NS | + |
| Comprehension | 8 | 18.50 | 5.90 | 8 | 18.75 | 4.27 | 0.14 | 7 | 0.89 | NS | + |
| Block Design | 8 | 24.50 | 11.75 | 8 | 22.88 | 9.86 | 0.55 | 7 | 0.60 | NS | - |
| Digit Symbol | 6 | 33.00 | 11.26 | 6 | 35.67 | 12.53 | 0.50 | 5 | 0.64 | NS | + |
| <i>Rey Complex Figure</i> | | | | | | | | | | | |
| Copy | 10 | 25.75 | 12.62 | 10 | 32.25 | 5.03 | 1.53 | 9 | 0.16 | NS | + |
| <i>Trail Making Test</i> | | | | | | | | | | | |
| Trails ‘A’ | 5 | 93.80 | 75.16 | 5 | 62.80 | 17.11 | 1.14 | 4 | 0.32 | NS | + |
| Trails ‘B’ | 3 | 113.67 | 63.26 | 3 | 112.67 | 51.86 | 0.05 | 2 | 0.96 | NS | + |

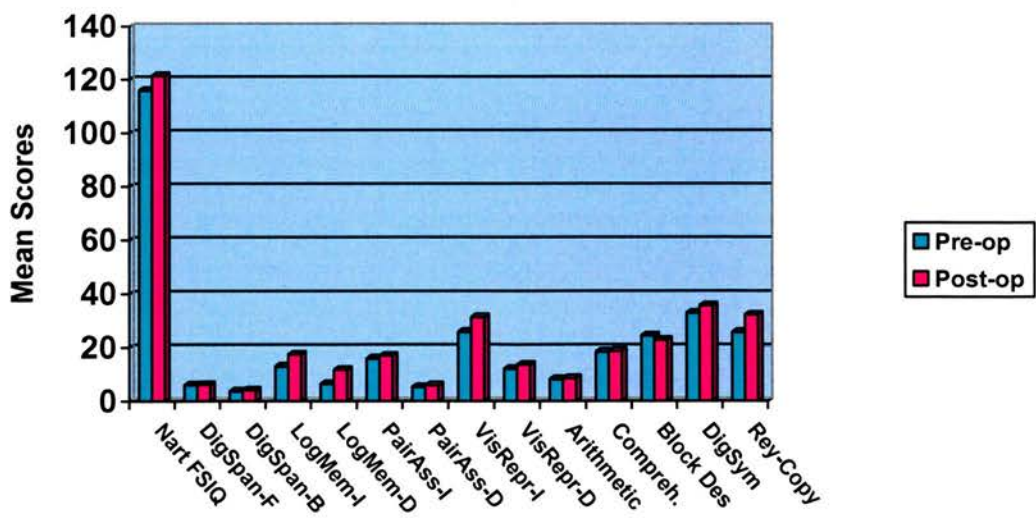
Note: NS = not significant ($p > 0.05$).

Note: Trend refers to the non-significant direction of improvement (+), or impairment (-).

3.2.6 (h) Summary of Results

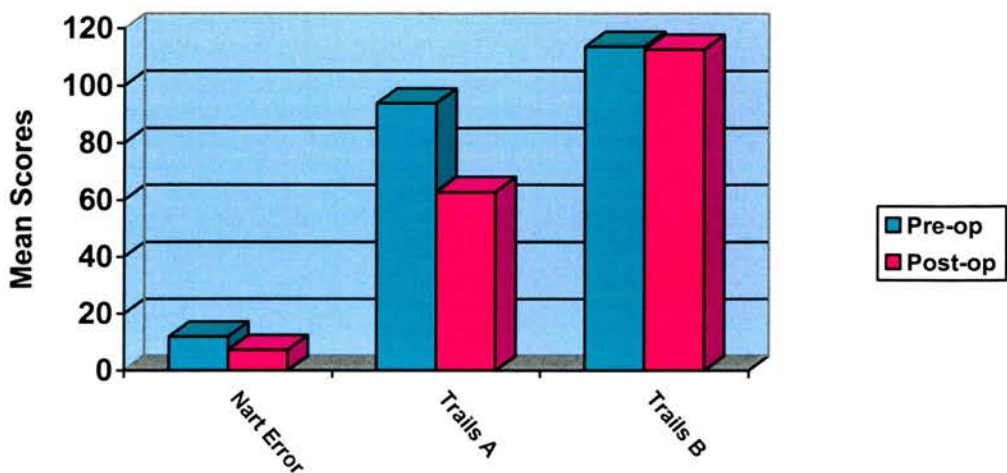
Paired samples *t*-tests revealed that there were no statistically significant differences, at the $p<0.05$ level, between the pre- and long term post-operative performance scores of the depressive disorder group, on any of the clinical neuropsychological subtests measuring general cognitive function. Mental state examination revealed that 80 per cent of the depressed group were considered to be fully orientated for time, place and person at the pre-operative stage, and 92 per cent at post-operative assessment. Examination of the trend of change at long term follow-up revealed a pattern of non-significant improvement in performance with the exception of one subtest. Given that the data represents both performance and error scores, visual illustration of such scores has been presented in two separate figures in order to ensure a consistent direction for indication of impairment. In Figure 5, improvement in performance is indicated by a post-operative increase in score, and impairment indicated by a decrease.

Figure 5. (Hyp. A) Clinical – Pre & Long Term Comparison – Depressive Disorder



Conversely, in Figure 6, improvement in performance is indicated by a post-operative decrease in score, and impairment indicated by an increase.

Figure 6. (Hyp. A) Clinical – Pre & Long Term Comparison – Depressive Disorder



3.2.6 (i) Clinical Assessment – Long Term Follow-Up - Other Diagnostic Categories

The following presentation of data represents the pre- and long term post-operative comparison of the clinical neuropsychological assessment of general cognitive function, regarding a total of 4 individuals who also underwent anterior capsulotomy for the treatment of diagnoses other than depressive disorder. One remaining individual with Bipolar Disorder also underwent the same procedure however there were no pre- or post-operative clinical neuropsychological assessment results available to report. An overview of the pre- and long term post-operative follow-up scores for each of the individual diagnostic categories is displayed in Table 11. As was the case with the larger depressive disorder group, minor fluctuation in performance between the pre- and post-operative assessments was evident across individuals and subtests. However, on the majority of subtests this fluctuation

reflected an improvement, through either a reduction in the number of errors made, or an increase in the total raw scores achieved. All individuals were noted to be fully orientated for time, place and person at both the pre- and post-operative stages.

Table 11. (Hyp. A) Clinical – Long Term Follow-Up – Other Diagnostic Categories

| General Cognitive Function Subtests | OCD (n=1) | | OCD & Bipolar (n=1) | | OCD & Depressive Disorder (n=2) | |
|--|--------------|-------------|------------------------|-------------|------------------------------------|-----------------|
| | Pre- Op | Post- Op | Pre- Op | Post- Op | Mean Pre- op | Mean Post-Op |
| <i>NART</i> | | | | | | |
| Error | 13 | 12 | 13 | • | 9.5 | 9.0 |
| FSIQ | 115 | 116 | 115 | • | 119 | 120 |
| <i>WMS-R</i> | | | | | | |
| Digit Span-Forward | 6 | 7 | 7 | 7 | 7.5 | 7.5 |
| Digit Span-Backward | 4 | 4 | 4 | 4 | 3.5 | 5 |
| Log. Memory-Imm. | 12 | 18 | 14 | 33 | 15.5 | 18 |
| Log. Memory-Del. | 2 | 14 | 13 | 25 | 9 | 12 |
| Paired Assoc.-Imm. | • | 6 | • | • | 18 | 20.5 |
| Paired Assoc.-Del. | • | 0 | • | • | 7.5 | 6.5 |
| Visual Reprod.-Imm. | 22 | 22 | 33 | 35 | 28.5 | 28.5 |
| Visual Reprod.-Del. | 0 | 6 | 24 | 27 | 22.5 | 21.5 |
| <i>WAIS-R</i> | | | | | | |
| Arithmetic | 4 | 4 | 12 | • | 11 | 8 |
| Comprehension | 6 | 6 | • | 24 | 30 | 31 |
| Block Design | • | 2 | 16 | 9 | 20.5 | 24 |
| Digit Symbol | • | • | • | 35 | 35.5 | 34.5 |
| <i>Rey Complex Figure</i> | | | | | | |
| Copy | 26 | 25 | 36 | 36 | 26 | 27.5 |
| <i>Trail Making Test</i> | | | | | | |
| Trails 'A' | 87 | 46 | 23 | 45 | 65.5 | 67.5 |
| Trails 'B' | • | • | 52 | 60 | 110.5 | 129 |

Note: (•) represents a missing data value.

3.2.7 Hypothesis B – Results

- **Hypothesis B:** Anterior capsulotomy will have an adverse effect on post-operative neuropsychological measures of executive function.

3.2.7 (a) Computerised Assessment – Short Term Follow-Up – Depressive Disorder

The following presentation of data represents the pre- and short term post-operative comparison of the computerised neuropsychological assessment of executive function, regarding a total of 17 individuals with major depressive disorder, who underwent treatment by Anterior Capsulotomy. An overview of the pre- and short term post-operative mean scores, standard deviations, and statistical comparisons is displayed in Table 12.

Table 12. (Hyp. B) CANTAB – Short Term Follow-Up – Depressive Disorder

| Executive Function Subtests | Pre-operative | | | Short Term Follow-Up | | | Paired Samples <i>t</i> -tests | | | Trend |
|---------------------------------------|---------------|-------|-------|----------------------|--------|-------|--------------------------------|----|---------|-------|
| | N | Mean | SD | N | Mean | SD | <i>t</i> | df | sig. | |
| <i>Stockings of Cambridge</i>† | | | | | | | | | | |
| Initial Thinking Time | 11 | 3.23 | 0.22 | 11 | 3.08 | 0.30 | 1.51 | 10 | 0.16 NS | +/- * |
| Subsequent Thinking Time | 11 | 2.69 | 0.37 | 11 | 2.70 | 0.37 | 0.17 | 10 | 0.87 NS | +/- * |
| Probs. Solved Min. Moves | 11 | 6.98 | 1.27 | 11 | 7.36 | 1.34 | 1.28 | 10 | 0.23 NS | + |
| <i>IED Shift</i> | | | | | | | | | | |
| Stages Completed | 12 | 6.42 | 2.94 | 12 | 5.25 | 3.50 | 1.68 | 11 | 0.12 NS | - |
| Total Errors | 12 | 24.75 | 12.14 | 12 | 23.17 | 9.94 | 0.52 | 11 | 0.62 NS | + |
| Pre-ED Errors | 12 | 17.33 | 13.06 | 12 | 16.83 | 11.05 | 0.26 | 11 | 0.80 NS | + |
| EDS Errors | 6 | 7.50 | 7.06 | 6 | 11.50 | 12.91 | 0.62 | 5 | 0.57 NS | - |
| Total Errors Adjusted | 12 | 89.33 | 77.66 | 12 | 116.92 | 91.01 | 1.48 | 11 | 0.17 NS | - |
| <i>Spatial Working Memory</i> | | | | | | | | | | |
| Between Search Errors | 12 | 52.67 | 19.36 | 12 | 56.75 | 23.89 | 0.68 | 11 | 0.51 NS | - |
| Total Errors | 12 | 56.00 | 20.48 | 12 | 59.83 | 27.29 | 0.58 | 11 | 0.57 NS | - |
| Between Errors – 4 boxes | 12 | 3.42 | 4.12 | 12 | 3.50 | 4.32 | 0.08 | 11 | 0.94 NS | - |
| Between Errors – 6 boxes | 12 | 16.00 | 10.08 | 12 | 18.25 | 9.43 | 1.15 | 11 | 0.27 NS | - |
| Between Errors – 8 boxes | 12 | 33.25 | 8.16 | 12 | 35.00 | 12.29 | 0.45 | 11 | 0.66 NS | - |

Note: NS = not significant ($p > 0.05$).

Note: **Trend** refers to the non-significant direction of improvement (+), or impairment (-).

† **Stockings of Cambridge:** Mean scores reported for Thinking Time subtests reflect log (10) transformations.

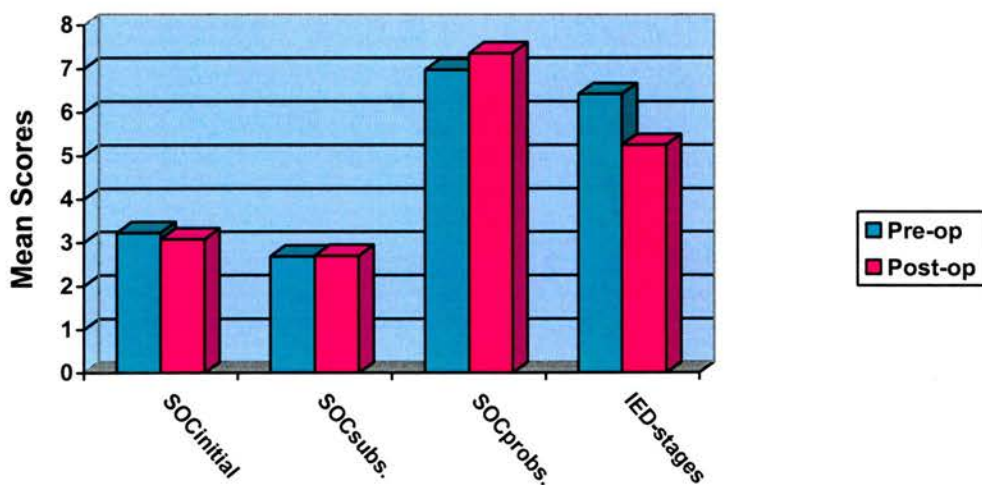
* **Stockings of Cambridge:** See Page 125 for discussion regarding the interpretation of this performance score.

3.2.7 (b) Summary of Results

Paired samples *t*-tests revealed that there were no statistically significant differences, at the $p<0.05$ level, between the pre- and short term post-operative performance scores of the depressive disorder group, on any of the computerised neuropsychological subtests measuring executive function. Examination of the trend of change at short term follow-up revealed a mixed pattern of non-significant improvement and impairment in performance scores, with a predominance of non-significant deficits at this stage.

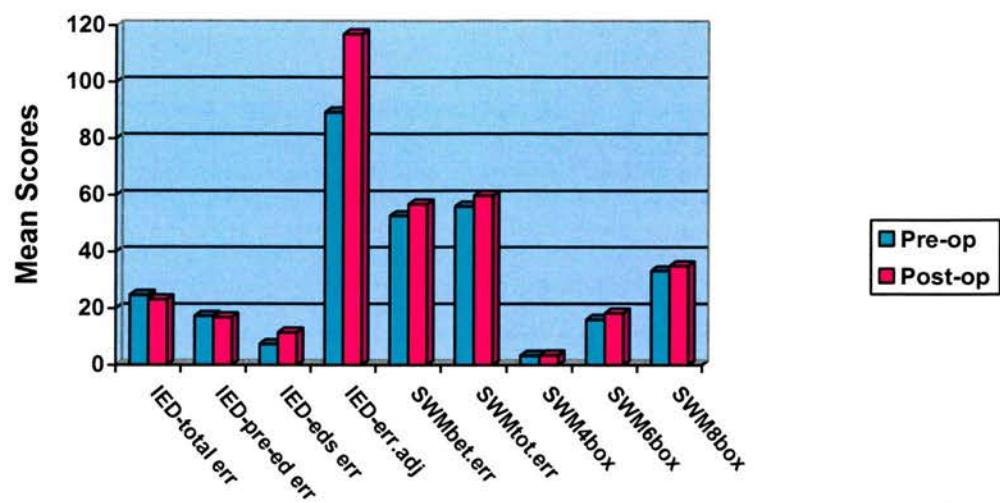
Given that the data represents both performance and error scores, visual illustration of such scores has been presented in two separate figures in order to ensure a consistent direction for indication of impairment. In Figure 7, improvement in performance is indicated by a post-operative increase in score, and impairment indicated by a decrease.

Figure 7. (Hyp. B) CANTAB – Pre & Short Term Comparison – Depressive Disorder



Conversely, in Figure 8, improvement in performance is indicated by a post-operative decrease in score, and impairment indicated by an increase.

Figure 8. (Hyp. B) CANTAB – Pre & Short Term Comparison – Depressive Disorder



3.2.7 (c) Computerised Assessment – Short Term Follow-Up – Other Diagnostic Categories

The following presentation of data represents the pre- and short term post-operative comparison of the computerised neuropsychological assessment of executive function, regarding a total of 5 individuals who also underwent anterior capsulotomy for the treatment of diagnoses other than depressive disorder. An overview of the pre- and short term post-operative follow-up scores for each of the individual diagnostic categories is displayed in Table 13. Visual inspection of this data revealed a similar pattern of results to that of the depressive disorder group. The minor fluctuation between pre- and post-operative scores appeared to reflect the presence of both improvement and impairment.

Table 13. (Hyp. B) CANTAB – Short Term Follow-Up – Other Diagnostic Categories

| Executive Function Subtests | OCD (n=1) | | Bipolar Disorder (n=1) | | OCD & Bipolar (n=1) | | OCD & Depressive Disorder (n=2) | |
|--|--------------|-------------|---------------------------|-------------|------------------------|-------------|------------------------------------|-----------------|
| | Pre- Op | Post- Op | Pre- Op | Post- Op | Pre- Op | Post- Op | Mean Pre-Op | Mean Post-op |
| <i>Stockings of Cambridge</i> † | | | | | | | | |
| Initial Thinking Time | 3.04 | • | 3.15 | 3.05 | 3.62 | 3.26 | 3.03 | 2.88 |
| Subsequent Thinking Time | 3.31 | • | 2.84 | 2.54 | 2.41 | 2.11 | 2.17 | 2.70 |
| Probs. Solved Min. Moves | • | 1.00 | 7.50 | 6.75 | 5.00 | 5.00 | 5.00 | 7.50 |
| <i>IED Shift</i> | | | | | | | | |
| Stages Completed | 8 | 7 | 6 | 5 | 9 | 9 | 7 | 9 |
| Total Errors | 36 | 30 | 38 | 46 | 21 | 12 | 29 | 13 |
| Pre-ED Errors | 5 | • | 38 | 46 | 5 | 8 | 27 | 8 |
| EDS Errors | 6 | • | • | • | 15 | 3 | 3 | 3.5 |
| Total Errors Adjusted | 36 | 55 | 113 | 146 | 21 | 12 | 79 | 13 |
| <i>Spatial Working Memory</i> | | | | | | | | |
| Between Search Errors | 107 | 75 | 73 | 58 | 13 | 21 | 36 | 40.5 |
| Total Errors | 109 | • | 78 | 58 | 13 | 24 | 40 | 43.5 |
| Between Errors – 4 boxes | 14 | • | 0 | 2 | 0 | 0 | 1 | 0 |
| Between Errors – 6 boxes | 34 | • | 26 | 21 | 0 | 8 | 15 | 12.5 |
| Between Errors – 8 boxes | 59 | • | 47 | 35 | 13 | 13 | 20 | 28 |

Note: (•) represents a missing data value.

† **Stockings of Cambridge:** Mean scores reported for Thinking Time subtests reflect log (10) transformations.

3.2.7 (d) Computerised Assessment – Long Term Follow-Up – Depressive Disorder

The following presentation of data represents the pre- and long term post-operative comparison of the computerised neuropsychological assessment of executive function, regarding a total of 5 individuals with major depressive disorder, who underwent treatment by Anterior Capsulotomy. An overview of the pre- and long term post-operative mean scores, standard deviations, and statistical comparisons is displayed in Table 14.

Table 14. (Hyp. B) CANTAB – Long Term Follow-Up – Depressive Disorder

| Executive Function Subtests | Pre-operative | | | Long Term Follow-Up | | | Paired Samples <i>t</i> -tests | | | Trend |
|--|---------------|--------|-------|---------------------|-------|-------|-----------------------------------|----|----------|-------|
| | N | Mean | SD | N | Mean | SD | <i>t</i> | df | sig. | |
| <i>Stockings of Cambridge</i> † | | | | | | | | | | |
| Initial Thinking Time | 3 | 3.38 | 0.29 | 3 | 4.29 | 0.09 | 7.95 | 2 | 0.02 SIG | +/- * |
| Subsequent Thinking Time | 3 | 2.75 | 0.39 | 3 | 3.10 | 0.38 | 2.77 | 2 | 0.11 NS | +/- * |
| Probs. Solved Min. Moves | 4 | 5.00 | 2.72 | 4 | 8.00 | 3.16 | 4.20 | 3 | 0.03 SIG | + |
| <i>IED Shift</i> | | | | | | | | | | |
| Stages Completed | 4 | 5.75 | 3.20 | 4 | 8.50 | 1.00 | 1.46 | 3 | 0.24 NS | + |
| Total Errors | 4 | 25.75 | 14.15 | 4 | 24.75 | 9.91 | 0.21 | 3 | 0.85 NS | + |
| Pre-ED Errors | 4 | 16.75 | 8.26 | 4 | 10.25 | 2.87 | 1.50 | 3 | 0.23 NS | + |
| EDS Errors | 2 | 12.00 | 12.73 | 2 | 18.50 | 12.02 | 13.00 | 1 | 0.05 SIG | - |
| Total Errors Adjusted | 4 | 107.00 | 72.76 | 4 | 31.00 | 21.80 | 1.84 | 3 | 0.16 NS | + |
| <i>Spatial Working Memory</i> | | | | | | | | | | |
| Between Search Errors | 4 | 63.50 | 15.42 | 4 | 69.50 | 20.60 | 0.71 | 3 | 0.53 NS | - |
| Total Errors | 4 | 70.00 | 17.17 | 4 | 70.75 | 20.02 | 0.09 | 3 | 0.93 NS | - |
| Between Errors – 4 boxes | 4 | 7.00 | 4.69 | 4 | 3.00 | 2.94 | 2.25 | 3 | 0.11 NS | + |
| Between Errors – 6 boxes | 4 | 20.25 | 6.13 | 4 | 23.00 | 3.46 | 1.29 | 3 | 0.29 NS | - |
| Between Errors – 8 boxes | 4 | 36.25 | 6.55 | 4 | 43.50 | 14.55 | 1.01 | 3 | 0.39 NS | - |

Note: NS = not significant ($p > 0.05$); **SIG** = significant ($p < 0.05$).

Note: **Trend** refers to the non-significant direction of improvement (+), or impairment (-).

† **Stockings of Cambridge:** Mean scores reported for Thinking Time subtests reflect log (10) transformations.

* **Stockings of Cambridge:** See Page 125 for discussion regarding the interpretation of this performance score.

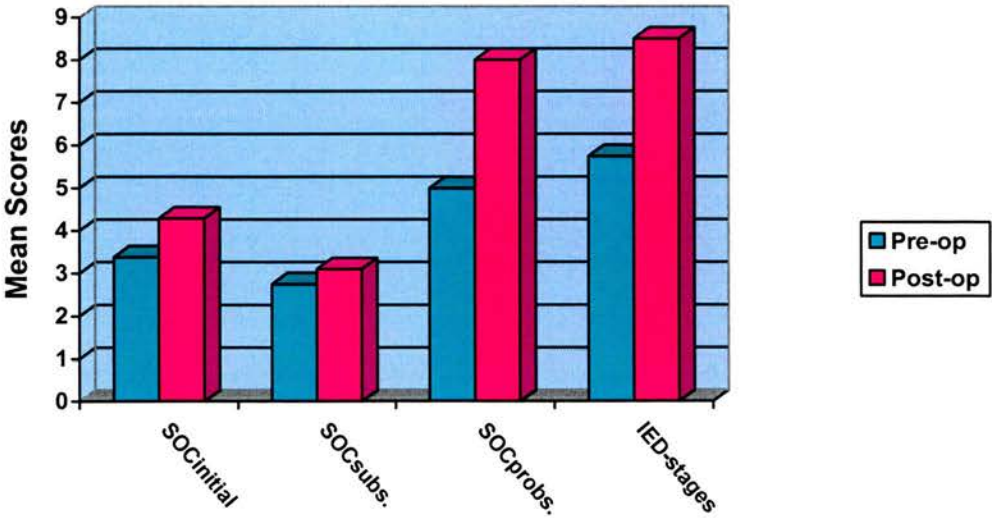
3.2.7 (e) Summary of Results

Paired samples *t*-tests revealed that a statistically significant increase, at the $p < 0.05$ level, was demonstrated on the Stockings of Cambridge subtest that measured initial thinking time [$t(2)=7.95$; $p < 0.05$]. Full discussion regarding the interpretation of this performance score can be found on page 125. Paired samples *t*-tests also revealed that a statistically significant improvement, at the $p < 0.05$ level, was demonstrated on the Stockings of Cambridge subtest that measured the number of problems solved in the minimum number of moves [$t(3)=4.20$; $p < 0.05$]. A statistically significant

impairment, at the $p<0.05$ level, was also demonstrated on the number of errors made at the extra dimensional shift stage, of the Intra/Extra-Dimensional Shift test [$t(1)=13.00$; $p<0.05$]. Caution must be applied in the interpretation of the latter result however given the small sample size on which it was based. No other subtest measuring executive function from the computerised neuropsychological assessment battery achieved statistical significance at this stage. Examination of the trend of change at long term follow-up revealed an approximately equal pattern of non-significant improvement and impairment in performance scores.

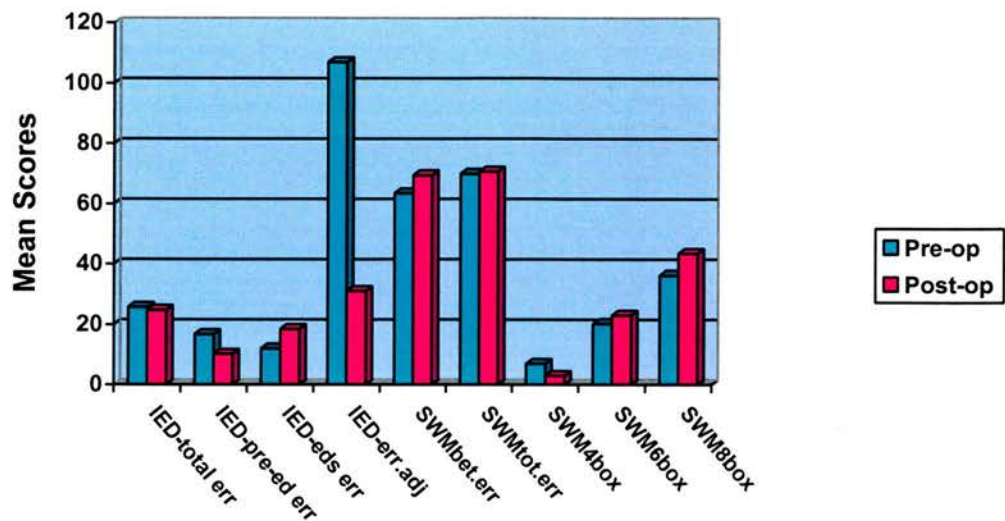
Given that the data represents both performance and error scores, visual illustration of such scores has been presented in two separate figures in order to ensure a consistent direction for indication of impairment. In Figure 9, improvement in performance is indicated by a post-operative increase in score, and impairment indicated by a decrease.

Figure 9. (Hyp. B) CANTAB – Pre & Long Term Comparison – Depressive Disorder



Conversely, in Figure 10, improvement in performance is indicated by a post-operative decrease in score, and impairment indicated by an increase.

Figure 10. (Hyp. B) CANTAB – Pre & Long Term Comparison – Depressive Disorder



3.2.7 (f) Computerised Assessment – Long Term Follow-Up – Other Diagnostic Categories

The following presentation of data represents the pre- and long term post-operative comparison of the computerised neuropsychological assessment of executive function, regarding a total of 4 individuals who also underwent anterior capsulotomy for the treatment of diagnoses other than depressive disorder. An overview of the pre- and long term post-operative follow-up scores for each of the individual diagnostic categories is displayed in Table 15. Visual inspection of this data revealed a similar pattern of results to that of the depressive disorder group. Minor fluctuation between the pre- and post-operative performance scores did occur across individuals and subtests reflecting a more equal pattern of improvement and impairment.

Table 15. (Hyp. B) CANTAB – Long Term Follow-Up – Other Diagnostic Categories

| Executive Function Subtests | OCD (n=1) | | Bipolar Disorder (n=1) | | OCD & Bipolar (n=1) | | OCD & Depressive Disorder (n=1) | |
|--|-----------|---------|------------------------|---------|---------------------|---------|---------------------------------|---------|
| | Pre-Op | Post-Op | Pre-Op | Post-Op | Pre-Op | Post-Op | Pre-Op | Post-Op |
| <i>Stockings of Cambridge</i> † | | | | | | | | |
| Initial Thinking Time | 3.04 | 3.68 | 3.15 | 4.32 | 3.62 | 4.41 | • | • |
| Subsequent Thinking Time | 3.31 | 3.66 | 2.84 | 3.95 | 2.41 | 1.27 | • | • |
| Probs. Solved Min. Moves | • | 6 | 7.50 | 7 | 5.00 | 12 | • | 4 |
| <i>IED Shift</i> | | | | | | | | |
| Stages Completed | 8 | 5 | 6 | 7 | 9 | 9 | 5 | 9 |
| Total Errors | 36 | 31 | 38 | 37 | 21 | 12 | 43 | 12 |
| Pre-ED Errors | 5 | 31 | 38 | 6 | 5 | 6 | 43 | 4 |
| EDS Errors | 6 | 0 | • | 31 | 15 | 5 | • | 7 |
| Total Errors Adjusted | 36 | 106 | 113 | 62 | 21 | 12 | 143 | 12 |
| <i>Spatial Working Memory</i> | | | | | | | | |
| Between Search Errors | 107 | 74 | 73 | 72 | 13 | 30 | • | 84 |
| Total Errors | 109 | 75 | 78 | 72 | 13 | 30 | • | 90 |
| Between Errors – 4 boxes | 14 | 8 | 0 | 5 | 0 | 0 | • | 0 |
| Between Errors – 6 boxes | 34 | 26 | 26 | 24 | 0 | 0 | • | 28 |
| Between Errors – 8 boxes | 59 | 40 | 47 | 43 | 13 | 30 | • | 56 |

Note: (•) represents a missing data value.

† **Stockings of Cambridge:** Mean scores reported for Thinking Time subtests reflect log (10) transformations.

3.2.7 (g) Clinical Assessment – Long Term Follow-Up - Depressive Disorder

The following presentation of data represents the pre- and long term post-operative comparison of the clinical neuropsychological assessment of executive function, regarding a total of 17 individuals with major depressive disorder, who underwent treatment by Anterior Capsulotomy. An overview of the pre- and long term post-operative mean scores, standard deviations, and statistical comparisons is displayed in Table 16.

Table 16. (Hyp. B) Clinical – Long Term Follow-Up – Depressive Disorder

| Executive Function Subtests | Pre-operative | | | Post-operative | | | Paired Samples <i>t</i> -tests | | | Trend |
|--------------------------------|---------------|-------|------|----------------|-------|------|--------------------------------|----|---------|-------|
| | N | Mean | SD | N | Mean | SD | <i>t</i> | df | sig. | |
| <i>Verbal Fluency Test</i> | | | | | | | | | | |
| ‘Animals’ category | 8 | 12.13 | 5.74 | 8 | 15.25 | 5.39 | 1.40 | 7 | 0.21 NS | + |
| ‘S’ category | 8 | 9.38 | 5.40 | 8 | 9.00 | 3.16 | 0.24 | 7 | 0.82 NS | - |

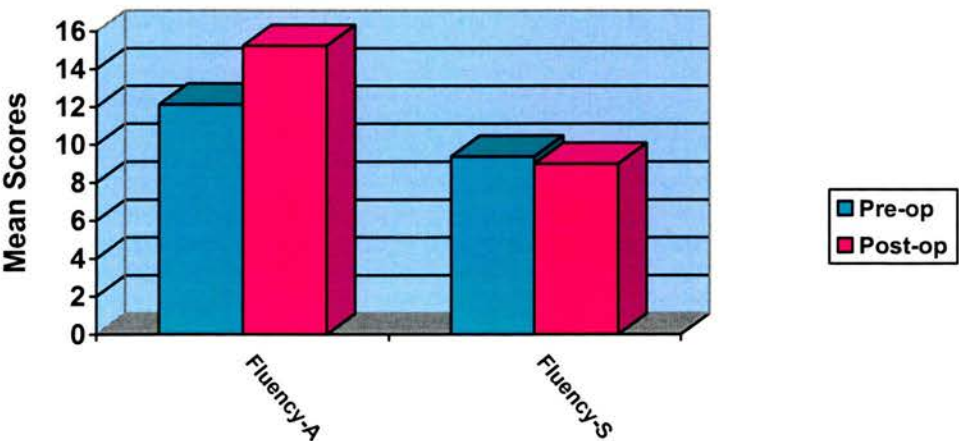
Note: NS = not significant ($p > 0.05$)

Note: **Trend** refers to the non-significant direction of improvement (+), or impairment (-).

3.2.7 (h) Summary of Results

Paired samples *t*-tests revealed that there were no statistically significant differences, at the $p < 0.05$ level, between the pre- and long term post-operative performance scores of the depressive disorder group, on any of the clinical neuropsychological subtests measuring executive function. Examination of the trend of change at long term follow-up revealed an equal pattern of non-significant improvement and impairment in performance scores. Visual presentation of these scores is illustrated in Figure 11, with improvement in performance indicated by a post-operative increase in score, and impairment indicated by a decrease.

Figure 11. (Hyp. B) Clinical – Pre & Long Term Comparison – Depressive Disorder



3.2.7 (i) Clinical Assessment – Long Term Follow-Up - Other Diagnostic Categories

The following presentation of data represents the pre- and long term post-operative comparison of the clinical neuropsychological assessment of executive function, regarding a total of 4 individuals who also underwent anterior capsulotomy for the treatment of diagnoses other than depressive disorder. An overview of the pre- and long term post-operative follow-up scores for each of the individual diagnostic categories is displayed in Table 17. As was the case with the larger depressive disorder group, minor fluctuation in performance between the pre- and post-operative assessments was evident across individuals and subtests, reflecting an approximately equal pattern of improvement and impairment in performance scores.

Table 17. (Hyp. B) Clinical – Long Term Follow-Up – Other Diagnostic Categories

| Executive Function Subtests | OCD (n=1) | | OCD & Bipolar (n=1) | | OCD & Depressive Disorder (n=2) | |
|--------------------------------|--------------|-------------|------------------------|-------------|------------------------------------|-----------------|
| | Pre- Op | Post- Op | Pre- Op | Post- Op | Mean Pre- op | Mean Post-Op |
| <i>Verbal Fluency Test</i> | | | | | | |
| ‘Animals’ category | 16 | 16 | 31 | 23 | 13.5 | 18 |
| ‘S’ category | 6 | 8 | 23 | 1 | 12.5 | 16.5 |

3.3 Results – Group B: Anterior Cingulotomy

To date, the total number of individuals who have undergone anterior cingulotomy as a first procedure currently amounts to three. Adequate pre- and post-operative neuropsychological data was available for only one individual, which therefore precluded any meaningful statistical analysis at this stage.

3.4 Results – Group C: Multiple Procedures

Similarly, despite there being a total of six individuals who have previously undergone anterior capsulotomy followed by anterior cingulotomy as a second procedure, there were only two individual cases in which adequate neuropsychological data was available. As such, statistical analysis of this group was not pursued at this stage.

CHAPTER 4 – DISCUSSION

CHAPTER 4 – DISCUSSION

4.1 Summary of Research

Neurosurgery for mental disorder continues to exist as one of a range of treatments available to individuals who experience severe and intractable forms of mental illness. For a number of reasons, this particular use of ablative neurosurgery has historically attracted a considerable amount of controversy. Despite modern advances in both technical procedure and understanding of the disorders currently indicated for consideration of NMD, the irreversibility of such physical treatments continues to attract interest from both public and professional groups alike. One of the greatest areas of discontent is associated with the underlying evidence base, as a result of considerable methodological problems within this field of research. Recommendations made in two recent reports which investigated the status and future of NMD within the UK, outlined the need for the establishment of a national database of patients undergoing such procedures (CRAG Working Group on Mental Illness, 1996; Royal College of Psychiatrists, 2000). Both reports highlighted the need for a long-term audit of outcome and adverse effects, including further neuropsychological research.

Therefore, the primary aim of the present study was to investigate neuropsychological outcome following neurosurgery for mental disorder. The entire population of 28 consecutive patients, who were treated by NMD at the Scottish centre between 1990 and 2003, was included in the present study. Following examination of the data set, the principal investigation focussed on a group of 22

individuals of mixed diagnoses, all of whom had undergone treatment by anterior capsulotomy. The comparison between individuals' pre- and post-operative neuropsychological performance, on both computerised and clinical assessments, was subsequently examined. Formal statistical analysis was conducted on the largest group of individuals, whose primary diagnosis was major depressive disorder. Descriptive accounts were subsequently provided for the smaller number of patients with alternative diagnoses. The forthcoming discussion therefore largely relates to the neuropsychological outcome following anterior capsulotomy in the treatment of major depressive disorder.

4.2 Hypothesis A - Summary of Results

- Anterior capsulotomy will have no adverse effect on post-operative neuropsychological measures of general cognitive function.

In order to address Hypothesis A, the comparison of pre- and post-operative neuropsychological performance scores, as measured through both computerised and clinical assessment of general functioning, was examined. Three measures of general cognitive function from the computerised battery of neuropsychological tests were investigated. To recap, participants' pre-operative computerised performance scores, assessed within an average of two weeks prior to the operation, were compared with those obtained at both short term follow-up, within an average of two weeks after surgery, and long term follow-up, an average of two and a half years post-operatively. A wide range of measures of general cognitive function from the clinical battery of neuropsychological tests was also investigated. Participants'

clinical performance scores, assessed within an average of two weeks prior to the operation, were compared with those obtained at long term follow-up, an average of one year post-operatively. The subtests included in the analysis of general cognitive function from both neuropsychological batteries are highlighted in Table 18.

Table 18. Clinical & Computerised Measures of General Cognitive Functioning

| Clinical Assessment Tests | Computerised Assessment Tests |
|------------------------------------|-------------------------------|
| - NART – error | - Pattern Recognition Memory |
| - NART – Full Scale IQ | - Spatial Span Length |
| - WMS-R – Digit Span | - Delayed Matching to Sample |
| - WMS-R – Logical Memory | |
| - WMS-R – Verbal Paired Associates | |
| - WMS-R – Visual Reproduction | |
| - WAIS-R – Arithmetic | |
| - WAIS-R – Comprehension | |
| - WAIS-R – Block Design | |
| - WAIS-R – Digit Symbol | |
| - Rey Complex Figure | |
| - Trail Making Test | |

Analysis of computerised neuropsychological performance scores at short term follow-up provided partial support for Hypothesis A. The present results suggested that there were no significant adverse effects in performance observed on the majority of tests which measured general cognitive performance, in the acute period following surgery. However, paired samples *t*-tests revealed that a statistically significant impairment was noted on two subtests from the Delayed Matching to Sample test. This impairment reflected a decrease in the total correct percentage achieved following a medium time delay, and a combined total of time delays.

Closer examination of the computerised neuropsychological results at short term follow-up revealed a trend of non-significant impairment in performance across all of the subtests which measured general cognitive function, with the exception of the Pattern Recognition Memory test which demonstrated a marginal, non-significant gain.

Analysis of computerised neuropsychological performance scores at long term follow-up provided full support for Hypothesis A. The present results suggested that there were no significant adverse effects in performance observed on any of the tests which measured general cognitive performance, when assessed following a longer period of time after surgery. In contrast, paired samples *t*-tests revealed that a statistically significant improvement was noted on one subtest from the Delayed Matching to Sample test. This improvement reflected an increase in the total correct percentage achieved following a medium time delay. On this occasion, closer examination of the computerised neuropsychological results at long term follow-up revealed a trend of non-significant improvement in performance across all of the subtests which measured general cognitive function, which is in contrast to the pattern observed following short term assessment.

Analysis of clinical neuropsychological performance scores at long term follow-up also provided full support for Hypothesis A. The present results suggested that there were no statistically significant adverse effects in performance observed on any of the tests which measured general cognitive functioning, when assessed following a longer period of time after surgery. Closer examination of the clinical

neuropsychological results at long term follow-up revealed a trend of non-significant improvement in performance across all of the subtests which measured general cognitive function, with the exception of the Block Design test. In summary, the trend of change observed on both computerised and clinical neuropsychological assessment measures, indicated an overall improvement in general cognitive performance, when assessed after a minimum period of one year following surgery.

4.3 Hypothesis A – Comparison with Previous Research

As previously highlighted in the introduction, a general consensus of opinion exists to support the assertion made in Hypothesis A. That is, there is little published evidence to support a deterioration in general cognitive functioning following any of the contemporary NMD procedures. Indeed, a trend of improvement in performance has previously been reported.

The overall results from the present study have demonstrated partial support for this hypothesis. On the vast majority of tests of general cognitive function, as measured by both computerised and clinical neuropsychological tests, participants performed at least as well after surgery, as they did before. The only significant adverse effects were observed in the acute period following surgery, approximately two weeks post-operatively, which demonstrated an acquired deficit on two visual memory subtests from the computerised neuropsychological assessment. However, when the same assessment was repeated at long term follow-up, approximately two and a half years from surgery, the results suggested that in comparison with pre-operative scores, performance had improved on both subtests, one of which reached statistical

significance. Therefore, these results are largely in keeping with previous published research.

The majority of early accounts which documented the general neuropsychological outcome following the procedure investigated in the present study, anterior capsulotomy, highlighted the stability or improvement of general cognitive functioning after surgery (Bingley et al, 1977; Lopez-Ibor & Lopez-Ibor, 1977; Rylander, 1979; Vasko & Kullberg, 1979). A small body of more recent research, designed specifically to investigate the neuropsychological outcome following anterior capsulotomy through the use of more extensive and advanced testing, has also arrived at similar conclusions. A recent study with close resemblance to the present one, investigated the pre- and post-operative neuropsychological performance of a group of individuals of mixed diagnoses (Nyman & Mindus, 1995). The authors concluded that performance on general measures of cognitive function remained intact when assessed one year following surgery. Two further capsulotomy studies made related claims regarding the post-operative stability of general cognitive functioning (Nyman et al, 2001; Ruck et al, 2003). Methodological differences between the latter two studies and the present research must however be borne in mind when drawing comparisons, as neither study had intra-individual pre-operative data with which to compare their results. Instead, long term follow-up data of capsulotomy patients on one of these studies was compared to the pre-operative performance of a separate group of individuals who were undergoing assessment for capsulotomy (Nyman et al, 2001).

As previously stated in the introduction, there appears to be little evidence to support the idea of specificity in effect regarding each of the current NMD procedures. This is illustrated by the similar conclusions which have been reported following investigation of neuropsychological outcome in studies related to each of the four contemporary interventions. For example, stability of performance on a range of general cognitive measures has previously been reported from research examining the outcome of anterior cingulotomy (Bailey et al, 1977; Ballantine et al, 1967; Brown & Lighthill, 1968; Corkin et al, 1979; Kim et al, 2003; Long et al, 1978; Martin et al, 1977; Meyer et al, 1973); subcaudate tractotomy (Broseta et al, 1979; Kartsounis et al, 1991); limbic leucotomy (Kelly, 1980; Mitchell-Heggs et al, 1976); and mixed operative groups (Cosyns et al, 1994; Cumming et al, 1995; Herner, 1961; Irle et al, 1998; Vasko & Kullberg, 1979). Once again however, it is important to emphasise that despite the remarkable consistency in general conclusions, there are, on closer inspection, substantial methodological differences between many of these studies, an issue which must be considered in the overall evaluation and interpretation of such research.

4.4 Hypothesis B – Summary of Results

- Anterior capsulotomy will have an adverse effect on post-operative neuropsychological measures of executive function.

In order to address Hypothesis B, the comparison of pre- and post-operative neuropsychological performance scores, as measured through both computerised and clinical assessment of executive functioning, was examined. Three measures of

executive function from the computerised battery of neuropsychological tests were investigated. To recap, participants’ pre-operative computerised performance scores, assessed within an average of two weeks prior to the operation, were compared with those obtained at both short term follow-up, within an average of two weeks after surgery, and long term follow-up, an average of two and a half years post-operatively. A small number of measures of executive function from the clinical battery of neuropsychological tests were also investigated. Participants’ clinical performance scores, assessed within an average of two weeks prior to the operation, were compared with those obtained at long term follow-up, an average of one year post-operatively. The subtests included in the analysis of executive function from both neuropsychological batteries are highlighted in Table 19.

Table 19. Clinical & Computerised Measures of Executive Functioning

| Clinical Assessment Tests | Computerised Assessment Tests |
|---------------------------|---------------------------------|
| - Verbal Fluency Test | - Stockings of Cambridge |
| | - Intra/Extra-Dimensional Shift |
| | - Spatial Working Memory |

Analysis of computerised neuropsychological performance scores at short term follow-up did not provide support for Hypothesis B. The present results suggested that there were no significant adverse effects in performance observed on any of the measures of executive functioning, when assessed in the acute period following surgery. Closer examination of the computerised neuropsychological results at short term follow-up revealed a mixed pattern of fluctuation in performance scores, reflecting both non-significant improvements and deficits across the range of

subtests. However, a predominance of non-significant deficits was observed on measures of executive function at short term assessment.

Analysis of computerised neuropsychological performance scores at long term follow-up provided partial support for Hypothesis B. The present results suggested that an adverse effect was observed on one of the subtests which measured executive functioning, when assessed following a longer period of time after surgery. Paired samples *t*-tests revealed that this result reflected acquired impairment observed in the number of extra-dimensional errors on the Intra/Extra-Dimensional Shift test.

However, the present results also revealed evidence which did not provide support for Hypothesis B. No significant adverse effects in performance were observed on a number of other subtests which measured aspects of executive function. In contrast, paired samples *t*-tests revealed that a statistically significant improvement was noted on one subtest from the Stockings of Cambridge test. This improvement reflected an increase in the number of problems solved in the minimum number of moves. A statistically significant increase in the initial thinking time taken on the Stockings of Cambridge test was also noted. Discussion regarding the interpretation of this result will follow shortly. Closer examination of the computerised neuropsychological results at long term follow-up revealed a trend of fluctuation in performance scores, reflecting an approximately equal pattern of both non-significant improvement and deficit on measures of executive function.

Analysis of clinical neuropsychological performance scores at long term follow-up did not provide support for Hypothesis B. The present results suggested that there were no significant adverse effects observed in performance on the subtests which measured executive functioning, when assessed following a longer period of time after surgery. Closer examination of the clinical neuropsychological results at long term follow-up also revealed a trend of fluctuation in performance scores, reflecting a more equal pattern of both non-significant improvement and deficit on measures of executive function at this stage.

4.5 Hypothesis B – Comparison with Previous Research

Given that the functional targets for neurosurgical intervention in NMD involve the interconnecting pathways between frontal brain regions and limbic structures, it raises the important question of whether deficits in executive function occur following contemporary neurosurgical procedures such as anterior capsulotomy, which was under investigation in the present study.

The prefrontal cortex, the area most widely implicated in conditions such as depression and OCD, is connected both directly and indirectly to an important network of brain regions involved in the realisation of emotion. Damage to such frontal areas of the brain often results in significant mood disturbance, as is frequently the case following the occurrence of a stroke, in which the severity of depression has been found to correlate significantly to the proximity of damage to the frontal region (House, Dennis, Mogridge, Warlow, Hawton & Jones, 1991; Robinson, Kubos, Starr, Rao & Price, 1984). The prefrontal cortex is also

responsible for the processing of 'executive functions', which are concerned with the management of human behaviour. These functions include effective planning, problem solving and reasoning abilities, as well as the awareness of surroundings, and the ability to monitor and adjust social behaviour according to internal or external cues (Lezak, 1993).

The neuropsychological sequelae of frontal lobe lesions, although often subtle on neuropsychological testing, can have a significant impact on daily functioning if they affect an individual's skills in a particularly salient aspect of their life. In the face of impaired general cognitive function, an individual may continue to lead an independent and fulfilling life providing their executive functions are not impaired. Conversely however, an individual is likely to experience widespread difficulties in independent daily functioning and social relationships if there has been damage to their executive function abilities, despite relatively intact general cognitive function (Lezak, 1995).

Initial evidence to support the hypothesis of executive dysfunction following NMD emanated from early outcome reports relating to the efficacy of many of the original psychosurgery procedures, which undoubtedly resulted in serious adverse effects on frontal lobe functioning and personality. More recent research using neuropsychological measures considered sensitive to frontal lobe function, has also added further weight to the hypothesis that executive dysfunction may occur in a proportion of patients following each of the main contemporary NMD procedures

(Corkin et al, 1979; Cumming et al, 1995; Irle et al, 1998; Kartsounis et al, 1991; Nyman & Mindus, 1995; Nyman et al, 2001; Ochsner et al, 2001; Ruck et al, 2003).

Recent research investigating the specific outcome of anterior capsulotomy on executive functioning has been reported by the Swedish NMD research group. The authors concluded in one study that deterioration in executive function was found in a proportion of patients of mixed diagnoses at one year follow-up (Nyman & Mindus, 1995). Another study reported that post-operative performance on tests of executive function fell within the lower average or mild impairment range (Nyman et al, 2001). A similar result was reported on a more recent study which highlighted lower than average results on tests of executive function, following a mean period of 13 years (Ruck et al, 2003). Despite the obvious relevance of the former research to the present study in terms of its examination of neuropsychological outcome following anterior capsulotomy, there are however significant differences which must be considered in comparing the general conclusions. The latter two studies employed a retrospective design which assessed individuals on neuropsychological measures after a designated follow-up period. Neither study had intra-individual pre-operative data with which to compare their results. Two of the studies were also conducted on patients who had a primary diagnosis of non-OCD anxiety disorders, including diagnostic categories that are not considered appropriate indications for NMD in the UK. This raises the possibility of diagnostic differences in neuropsychological performance, and further limits the comparisons which can be drawn with the present study.

Further evidence to suggest post-operative disturbance in executive function has also been reported following each of the other contemporary neurosurgical procedures: namely, anterior cingulotomy (Corkin et al, 1979; Ochsner et al, 2001); subcaudate tractotomy (Kartsounis et al, 1991); and mixed-operative procedures (Cumming et al, 1995; Irle et al, 1998). Again, caution must be applied in making comparisons with the present results due to the different procedures and diagnostic groups under study, and the different experimental designs employed. In addition to the neuropsychological research, evidence to support negative changes in post-operative personality functioning have also been reported (Goktepe et al, 1975; Herner, 1961; Kullberg, 1977; Strom-Olsen & Carlisle, 1971; Vilkki, 1977).

The overall results from the present study have demonstrated partial support for the executive dysfunction hypothesis. At long term follow-up on the computerised neuropsychological assessment, an acquired deficit on one of the executive function subtests was observed. However, closer examination of this result highlighted that although a significant increase was observed in the number of extra-dimensional shift errors on the Intra/Extra-Dimensional shift test, the conclusions which may be drawn from this are considerably limited, in light of the fact that this result was based on the performance of only two individuals. Whilst the possibility exists that this does represent a true impairment on this aspect of executive functioning, it should also be noted that the combined total of all errors made on the Intra/Extra-Dimensional Shift test, did not in itself display a statistically significant change at long term post-operative assessment.

The second significant result noted at long-term follow-up reflected an increase in the mean initial thinking time taken on the Stockings of Cambridge test, a measure generally thought to reflect individuals' planning ability. Such an increase in thinking time could be interpreted in two contrasting ways. Firstly, it could be interpreted as an acquired deficit, with the increase in planning time taken to reflect greater difficulty in problem solving, or a lack of initiation. Alternatively, it could be interpreted as an improvement in executive functioning, with longer thinking time taken to reflect a more careful and well thought-out response to problem solving, or a decrease in impulsivity.

The third significant result from the long term follow-up computerised neuropsychological assessment may shed further light on the former issue. A significant increase in the mean number of problems solved, in the minimum number of moves, was observed on another of the Stockings of Cambridge subtests. This result reflects a significant improvement in individuals' ability to apply the most effective strategy on a test of problem solving. This could therefore be proposed as supporting evidence for the latter of the two interpretations outlined above. That is, the increase in planning time taken could in the case of the present study, reflect a more positive pre-planned response, in light of the significant improvement observed in the overall task performance. The clinical implications of the Stockings of Cambridge test may therefore require consideration on an individual basis, with corroboration from performance on additional measures of assessment. This also highlights the advantage of conducting more than one manner of neuropsychological assessment.

The result from the latter subtest, in which there was a significant post-operative improvement in the overall number of problems solved, has considerable ‘real-life’ implications. A large proportion of individuals who proceed to surgery have a history of long periods of hospitalisation, and reliance on relatives and carers. Improvement of the type noted on this test has the potential to facilitate positive changes in the level of dependence these individuals have on other people, and make a functional difference to their daily lives. This in turn has the potential to contribute towards the development of an increasing sense of control and achievement in a wider range of circumstances.

With regard to the present study, further examination of performance on the computerised neuropsychological assessment at short term follow-up, and the clinical neuropsychological assessment at long term follow-up, both revealed that participants performed as well after surgery as they had pre-operatively, on the measures of executive function assessed. These results, combined with the suggestion of some improvement on a small number of subtests, as previously discussed, are therefore not entirely in keeping with some of the previous literature.

Despite the suggestion of post-operative executive dysfunction outlined in a number of studies, the lack of any such change has also been reported (Kim et al, 2003; Long et al, 1978). Indeed, the former study reported improvement on several subtests measuring executive function in OCD patients at twelve month follow-up, through a reduction in the number of errors made post-operatively. This has been supported by a number of studies which have demonstrated an absence of negative personality

change following surgery (Bingley et al, 1977; Bridges et al, 1994; Kelly, 1980; Lopez-Ibor & Burzaco, 1972; Mindus & Nyman, 1991; Mindus et al, 1999; Mindus et al, 1988; Rylander, 1979; Sachdev & Hay, 1995). Additionally, in research on which impaired post-operative executive functioning has been reported (Nyman et al, 2001; Ruck et al, 2003), the authors have suggested that such impairment may not simply be interpreted as a direct result of the surgical procedure involved. Rather, they point out reports in which the pre-operative performance of individuals awaiting NMD procedures have also been noted to fall within the lower normal to mild impairment range (Kartsounis et al, 1991; Nyman et al, 2001). Another explanation which has been postulated to account for the observation of post-operative disturbance in cognitive function, particularly within the acute phase following surgery, is that relating to the effect of transient oedema. This has been highlighted in two studies which documented the improvement in executive functioning when assessed following a longer time period after the operation (Kartsounis et al, 1991; Nyman et al, 2001).

In summary, the results outlined in the present study have not purely reflected an adverse effect on executive function, as may be suggested by some of the existing literature. It must however be reiterated that to date, the number of studies which have specifically examined executive functioning is extremely small, therefore comparisons between such research and the present study are subsequently limited by many of the methodological issues which have formerly been discussed. However, the important principle which can be identified is an acute awareness of the potential for impairment in executive functioning following any of the

contemporary NMD procedures, which has significant clinical and research implications.

4.6 Clinical Implications

A significant issue highlighted through the investigations conducted in the present study is that regarding appropriate test selection in the clinical neuropsychological assessment of this population group. The process of compiling a database of performance scores has demonstrated the range of subtests which were clearly beyond the abilities of the majority of patients with this degree of psychiatric illness. This has been a useful discovery for the clinicians involved in the assessment process as it is difficult to gauge this sort of information when the total number of annual NMD referrals is so few.

Significant practical and resource implications have also been highlighted regarding the ongoing maintenance of the clinical database which was established for the purpose of the present study. Following recent recommendations and guidelines for best practice in the provision of NMD services (CRAG Working Group on Mental Illness, 1996; Royal College of Psychiatrists, 2000), the future status and availability of neurosurgery for mental disorder will be heavily dependant on the demonstration of ongoing audit and research, including publication of both efficacy results, and the presence or absence of adverse effects. As the process of NMD has potentially significant implications for aspects of neuropsychological functioning, pre- and post-operative assessment of all new surgical cases, as well as ongoing follow-up of participants included in the present study, will be of paramount importance. This

therefore requires that the clinical database is maintained and updated with all new information, something which has to date proved extremely difficult for the existing clinicians, given the lack of any funded clinical or research investment in the service. Therefore, significant organisation and change will be required in the practice of recording such outcome information, in order that vital data is not lost or overlooked in future years.

The extent of the debate regarding the important role and potential impairment of frontal lobe function following NMD, has also highlighted the need to further investigate the availability of neuropsychological assessments which are sensitive to the often subtle effects of executive dysfunction. It is no longer acceptable to rely solely on measures of general cognitive function with this patient group, following reports that individuals with frontal lobe damage often perform within the average range on such tests (Stuss & Benson, 1986). To ensure the future assessment of a wide range of cognitive functions, by the most valid and reliable methods available, it may therefore be helpful to conduct a regular review of test selection and rates of completion, as well as keeping abreast of new developments in the field of neuropsychological testing.

Closer examination of the statistical results and the overall trend of change observed in the present study has highlighted the crucial importance of timing in the assessment of this particular population group, which has significant clinical and research implications. As the results of the present study demonstrate, a different pattern of statistically significant and non-significant changes in performance were

noted, in the comparison of pre- and post-operative measurement of general and executive function, at the short and long term assessment stages. In a similar study to the present one, the issue of timing in the assessment of outcome has also been highlighted (Kartsounis et al, 1991). The authors examined performance on a range of general and executive function tests pre-operatively, in the immediate post-operative stage, and at six months follow-up. Significant deterioration in performance on subtests of both general and executive function was reported at the acute assessment stage, which at longer term follow-up was noted to have returned to the previous pre-operative levels. More recently, investigation of neuropsychological performance following anterior capsulotomy was reported (Nyman et al, 2001). Results demonstrated post-operative deterioration on a measure of executive function, which was reflected by the lower number of categories completed on the test. However, the authors also reported the observation of a positive correlation between the time elapsed following surgery, and the number of categories completed. This was proposed as evidence for the restoration of executive function following a longer follow-up period.

Transitory effects of post-operative oedema are the most commonly cited explanation for the seemingly transient deterioration often reported following assessment in the acute phase after surgery. The overall pattern of performance scores therefore illustrates the importance of conducting neuropsychological, and other related assessments of outcome, following an adequate time period which is generally considered to be approximately one year after surgery. This estimation is based on the observation that a typically gradual process of recovery occurs over the

period of the first year following surgery, in the majority of patients who demonstrate improvement (Cobb & Kelly, 1990; Fenton, 1998; Poynton et al, 1988).

4.7 Theoretical Implications

Central to the ongoing debate regarding the continuing availability of ablative procedures in the treatment of mental disorder, is the crucial issue of whether NMD actually works. A further issue to consider in this scenario is whether there is a negative price to pay in terms of adverse effects, in return for any symptom relief which may be gained. At present, a significant amount of uncertainty continues to surround the underlying mechanisms by which these neurosurgical procedures exert their effect.

Results obtained in the present study suggest an overall stability of cognition on measures of general and executive function following treatment by anterior capsulotomy, with relatively few fluctuations in performance observed. The general trend of change highlighted non-significant improvement on the vast majority of measures of general cognitive functioning at follow-up periods exceeding one year, and was entirely in keeping with previous research. Again, a similar stability of performance was observed across the vast majority of measures of executive functioning, with a suggestion of both significant and non-significant minor fluctuations in performance at long-term follow-up.

The results obtained in the present study suggest tentatively that significant adverse neuropsychological effects were not experienced by the current cohort of patients,

nor does there appear to be any specific pattern of neuropsychological functions which are commonly affected. This in itself is a fascinating finding, in light of the nature of invasive neurosurgery these individuals have undergone. It is therefore interesting to consider why these individuals do not display the adverse effects which may be expected, in light of our understanding of human neuropsychology. Several explanations have been proposed in an attempt to answer such questions, and are broadly divided into those which are directly associated with the effects of surgery, and those which appear unrelated to the specific surgical influences. The latter will be discussed first.

It has generally been assumed that post-operative improvements in neuropsychological functioning are most likely to be the result of increased attentional capacity, following symptom relief after surgery. The present results were reported independently of any analysis of symptomatic outcome, therefore correlations between the two cannot be made at this time. This would however be an important area of interest to consider in future research projects.

It has also been suggested that an increase in attentional capacity following surgery may be the consequence of a gradual reduction in medication, and effects of other treatments such as ECT, in the prelude to surgery (Jenike, 1998; Joschko, 1986). Given the complexity of the issue regarding the effects of medication on cognitive functioning (Lezak, 1995), this presents an extremely valid consideration, particularly with regard to assessments conducted in the acute period immediately following surgery. In light of the likely continued reduction in medication in cases in

which NMD is observed to have had a positive outcome, this may also be considered to account for some of the neuropsychological improvement noted at longer term follow-up.

A number of other potentially confounding effects which typically have not been methodologically controlled for in NMD research and which may also produce a confounding effect on neuropsychological functioning at the pre- and post-operative assessment stages, include the grouping together of patients who may differ substantially in demographic variables such as age, gender, level of education, premorbid intellectual ability, and socio-economic status. This may potentially result in a blurring of actual neuropsychological effects where present, and lead to overgeneralizations. Individuals are also likely to vary considerably in terms of the range and nature of pre-operative treatments and periods of hospitalisation, as well the extent and adequacy of post-operative rehabilitation. Whilst appreciating the potential contribution such factors may have in any measure of outcome following NMD, dissociating the effects of these variables would prove to be extremely difficult, in light of the rarity of this population, and the inevitable reduction in power of any statistical evaluation which was to attempt to separate out these variables.

It is of course also possible that the results obtained may reflect the insensitivity of the tests employed. The difficulty in detecting subtle changes with available measures of executive function in particular, has been raised within the literature (Lezak, 1993). This is an important issue which has significant clinical implications,

as previously discussed. The present study attempted to minimise this possibility through the inclusion of a broad range of measures of both general cognitive and executive functioning, administered in two independent formats.

Investigation of the difference between the pre- and post-operative neuropsychological performance on a range of cognitive assessments inevitably involves repeated examinations. This ultimately raises the issue of practice effects as a potential factor in accounting for the stability or improvement of neuropsychological performance after surgery. Research has demonstrated a significantly greater influence of repeated assessments on tests involving a large speed component, learning, and those which are answered with a single solution (Lezak, 1995). The confounding effects of serial testing were however minimised in the present study: both in the clinical neuropsychological assessments, in which the time delay between testing was approximately one year; and on the computerised assessments, where parallel forms were used where possible on follow-up examinations.

Whilst the exact mechanisms by which NMD is known to exert its effect remain unclear, the possibility of a placebo response must also be considered. Indeed, whilst the general progression of clinical improvement in NMD is typically observed over a period of months to years following surgery (Fenton, 1998), initial dramatic improvements which are not maintained have also been reported (Poynton, Kartsounis & Bridges, 1995). It is therefore possible that a placebo response may be attributable in a proportion of cases in which such early responses are observed,

however this would appear to be extremely unlikely to account for the larger majority of cases in which improvement is sustained at long term follow-up (Bridges et al, 1994; Cobb & Kelly, 1990; Hay et al, 1993).

In summary, it would appear that whilst the previous non-surgical influences highlight important issues for consideration in the interpretation of any piece of research in the field of NMD, including the present study, it does however appear unlikely that any of these individual factors alone could account for the relative consistency in reports of long term improvement.

In evaluating all potentially contributing factors in the consideration of the overall effects of NMD, a number of potential explanations have been put forward which suggest the possibility of change via a direct surgical effect. It is possible therefore that general improvement following surgery may occur as a consequence of neuroanatomical, neurochemical, or neuroendocrine changes within the brain (Marino & Cosgrove, 1997).

Recent evidence has demonstrated neurophysiological changes in the brain regions targeted by each of the NMD procedures, in cases of major depressive disorder (Drevets, Price, Simpson, Todd, Reich, Vannier et al, 1997; Drevets et al, 1992; Goodwin et al, 1993; Hornig et al, 1997; Ketter et al, 2001; Soares & Mann, 1997; Steffans & Krishnan, 1998) and OCD (Kang et al, 2003; Rauch & Baxter, 1998; Saxana & Rauch, 2000; Trivedi, 1996). This evidence raises the possibility that these regionally specific areas may not in fact be structurally or functionally

‘healthy’ in their pre-operative state, in chronic cases of these disorders. Considered from this angle, the fact that significant post-operative deleterious effects of NMD are generally not found, it is perhaps less surprising, as this recent evidence would suggest that distinct areas of brain functioning are already adversely affected by the nature of the disorders experienced, prior to surgery.

Indeed, evidence has suggested that the neuropsychological performance of a proportion of patients with intractable OCD was noted to fall within the lower normal to mild impairment range at pre-operative assessment (Kartsounis et al, 1991; Nyman et al, 2001). This is supported by an accruing neuropsychological evidence base which has demonstrated a range of cognitive deficits of variable nature and severity, in cases of depression (Franke et al, 1993; Golinkoff & Sweeney, 1989; Porter et al, 2003; Purcell et al, 1997), and OCD (Boone et al, 1991; Greisberg & McKay, 2003; Head et al, 1989; Okasha et al, 2000). This point of interest raises many further issues regarding one of the most fundamental debates surrounding this particular use of neurosurgery; that is, whether brain regions targeted for destruction in NMD represent ‘healthy’ tissue, as has previously been assumed. Such accumulating evidence would appear to suggest that this perspective is now somewhat outdated.

In summary, the likelihood exists that a range of both surgical and non-surgical factors contribute to the general effects of neurosurgery in the treatment of mental disorder. Delineating the separate effects has so far proved to be impractical;

therefore, consideration of all potentially contributing influences must be taken into account in the evaluation of any aspect of outcome research within this field.

4.8 Limitations

As highlighted in the introduction, there are several methodological considerations which must be taken into account in the overall consideration of results obtained in the present study. Whilst attempts have been made to address many of the common criticisms levied at the general NMD literature base, it is nonetheless very difficult to avoid them all in such research, given the very select population group under study.

One of the most commonly cited downfalls associated with NMD research, and indeed of the present study, is the absence of non-surgical or sham control groups with which to compare the surgical data. Although attempts at conducting prospective, randomised controlled studies have previously been made (Baer et al, 1995; Fodstad et al, 1982; Kullberg, 1977), conclusions have been limited by the inherent difficulties relating to the adequacy and appropriateness of using control groups in research with this population group. Indeed, there are pertinent ethical and practical objections to this, which would make a fully randomised double-blind study extremely difficult, if not impossible (CRAG Working Group on Mental Illness, 1996; Royal College of Psychiatrists, 2000). The very fact that NMD is considered to be a treatment of last-resort indicates the level of illness severity and chronicity experienced amongst those considered to be suitable candidates. Given the high level of morbidity and potential mortality in such cases, the idea of employing a waiting list control group raises significant ethical issues (Binder & Iskandar, 2000;

Jenike, 1998). There are also considerable ethical implications associated with the proposal of sham surgical groups, again for the reason that it extends the period of time before an individual receives 'treatment' per se, and also as such a procedure would still require a craniotomy to be conducted, which is not without its accompanying risks.

There are a number of practical difficulties associated in identifying alternative control groups for the purpose of comparison. The number of individuals who are considered suitable for surgery and who subsequently refuse, are so small that it would be unfeasible to consider these individuals as controls (Poynton et al, 1988). Alternatively, another potential group would be those with similar diagnostic features, who had not been referred for surgery. This however has also proved to be extremely difficult, as not only would the groups require to be matched for diagnosis and typical demographic details, but also for additional important factors which affect this group, including length of illness, current presentation, previous range of treatments and periods of hospitalisation (Kartsounis et al, 1991; Poynton et al, 1988). As such, in the absence of the 'ideal' prospective, randomised controlled trial, a general consensus appears to support the use of intra-individual, pre- and post-operative comparisons within cohorts of surgical patients.

Another important limitation affecting the conclusions which may be drawn from the present study is that relating to the small number of participants involved in the statistical analysis. The effect of having such a small group is a reduction in the statistical power available to detect small and medium sized effects where they occur

(Clark-Carter, 1997). Retrospective power calculations suggested that the analysis performed with the current sample of participants would be limited to detecting very large effects where present. It is entirely possible therefore that small or medium sized effects were also present, but were not detected as a result of the sample size. For example, the positive non-significant trend reported in general cognitive function following long term clinical and computerised assessments, may have reached significance with a larger participant group. This issue is however inevitable in the evaluation of a neurosurgical procedure which is performed in a limited number of specialist centres worldwide, with an extremely rare population group. For example, in the period between 1990 and 2000, a total of 62 referrals were made to the NMD service in Dundee, of which 28 proceeded to have surgery (Matthews & Eljamel, 2003). Unfortunately, the reasons for which some candidates were found to be unsuitable for surgery were also the same reasons that these individuals would be unsuitable as a control group. However, the population in the present study was the entire consecutive group of patients accepted for surgery over a thirteen year period to a national centre for the practice of NMD.

In light of the relatively large number of statistical analyses which were performed in the present study, it must be acknowledged that the small number of statistically significant results observed, could of course be considered to have arisen through chance. This explanation would however appear less likely given the similarity of the trend of change in the present study, and the type of pattern reported in a significant amount of previous research.

Another issue to consider in the context of the present study is that regarding the timing of pre-operative assessments, which took place within an average of two weeks prior to surgery. It could be argued that patients may experience heightened anxiety in the days leading up to surgery, which may potentially confound their pre-operative test results. Conversely however, it has also been suggested that patients may in fact be less emotionally disturbed at this stage, as a result of their increased hopes and expectations that the surgery will have positive consequences for them (Long et al, 1978). Anecdotally, the latter has most often been the experience noted by the clinicians involved in conducting such assessments. The most obvious solution in addressing this issue would be to compare assessments taken several months before surgery, to those conducted more typically in the days before surgery. This scenario would however present additional challenges as many of the patients are tertiary referrals, and such specialist assessments may not be available in their referring area. In cases where such services were available, further issues could be raised regarding the consistency in approach, as a result of an additional number of test administrators involved.

With regard to the timing of the post-operative assessments, the issue of testing in the acute post-operative phase is also worthy of consideration. Computerised assessments have typically been conducted within an average of two weeks following surgery, before the patient returns back to their referring area. The acute physiological effects of neurosurgery cannot confidently be ruled out as continuing to have a lingering effect on an individual's neuropsychological performance at this stage (Herner, 1961). Assessment in the acute phase is however extremely important

in providing a post-operative marker of cognitive function, to which pre-operative data, and longer term follow-up assessments can be compared. In light of the evidence which suggests a gradual step-wise progression of improvement in NMD cases (Cobb & Kelly, 1990; Fenton, 1998), this thereby allows for investigation of the difference in cognitive performance at designated time points following surgery. Initial evidence of long term follow up performance for a small number of individuals was outlined in the present study. Current procedure requires that neuropsychological assessments are conducted for all patients at yearly intervals following surgery. In time this process will enable such analysis to be conducted in larger numbers, for both computerised and clinical neuropsychological assessments.

4.9 Strengths

In view of the limitations associated with the present study, the conclusions which may be drawn remain tentative. The current study has however attempted to address some of the common criticisms made of previous studies within this field of research, and fulfils several of the key criteria for appropriate evaluation of NMD, as outlined in the literature (Snaith, 1994).

Each individual who underwent NMD at the Scottish centre was considered to have been carefully selected, with close attention paid to the confirmation of diagnosis and assessment of previous treatment adequacy. An intra-individual experimental design was employed, and a broad range of valid and reliable psychometric measures had been administered. The results of neuropsychological assessment conducted at three separate time points were investigated, two of which took place a minimum of one

year following surgery. The present study reported on the results of a complete sample of patients who had undergone NMD, thereby reducing the probability of measuring a select sample of willing volunteers. Each diagnostic group was statistically analysed and reported upon separately, in order to control for the potentially confounding effects of subgroup differences. In contrast to many of the existing studies within this field of research, the sample of participants included in the present study had all undergone only one neurosurgical procedure at the time of assessments thereby reducing the potentially confounding effects of additional interventions.

A recurring criticism of the published literature is that relating to the lack of independent investigation of outcome, with the clinicians responsible for selecting NMD candidates often also solely responsible for conducting the outcome assessments. Thus, a considerable strength of the present study was that neuropsychological assessment had been achieved through the use of two independent approaches. The first involved assessment by a clinician who had very little previous information regarding each patient, other than their primary diagnosis. The second, conducted at a different time, involved a computerised assessment administered by a technician who had no prior knowledge of patient details. In this context therefore, the present study has demonstrated that two alternative approaches to neuropsychological assessment, conducted in different locations by different people, using different measures assessing functionally overlapping skills, has produced similar results.

The present study is the first of its kind to report the results of such a wide range of neuropsychological measures of assessment, including the use of the CANTAB test battery in addition to a clinical assessment. To date, it is also the largest study to report on neuropsychological outcome following anterior capsulotomy in the treatment of major depressive disorder. The only previous outcome research conducted with this specific procedure and diagnostic group was conducted over forty years ago, on a markedly heterogeneous group of 19 depressive disorder patients (Herner, 1961).

4.10 Future Research

Any physical intervention performed in the treatment of psychiatric disorders is likely to continue to attract both inquiry and controversy. In the case of NMD, the irreversible nature of the procedures involved, and acknowledged limitations regarding its underlying rationale and evidence base, further increase both public and professional interest. Continued evaluation of the efficacy of NMD and the presence of adverse effects is therefore of paramount importance. Despite the methodological limitations inherent in conducting research within this unique population group, there are significant clinical, ethical and scientific reasons to support the ongoing need for further research (Mindus et al, 1994b).

To date, with regard to neuropsychological research, there has been no clear evidence to suggest predicting factors of outcome following NMD. Continued investigation that is prospectively structured to detect adverse effects with precise neuropsychological measurement, is therefore required. Recent good practice

guidelines highlighted the importance of an extended period of assessment and indefinite long term follow-up for this patient group (CRAG Working Group on Mental Illness, 1996; Royal College of Psychiatrists, 2000).

With particular regard to the surgical activities conducted at the Scottish centre, there are a number of interesting research possibilities. At present, anterior capsulotomy is offered in cases of treatment refractory OCD, whilst anterior cingulotomy is offered in cases of intractable depressive disorder. This recent change in practice is due largely to the technical preference of the Consultant Neurosurgeon involved. Consequently, with a rise in the population size of the anterior cingulotomy group over the forthcoming years, which currently amounts to three, this should enable a procedural comparison of the neuropsychological effect of cingulotomy on depressive disorder, with the neuropsychological effect of capsulotomy on depressive disorder, as was investigated in the present study. Similarly, with anterior capsulotomy currently being performed as the treatment of choice in refractory OCD, this should in time allow for comparison between the neuropsychological effect in such cases, and the cohort of patients treated by anterior capsulotomy for refractory depressive disorder in the present study.

In light of the previously outlined difficulties in detecting small or medium sized effects as a result of the small population sample size inherent with this type of surgery, possibilities for future research may exist through the collaboration of national and international NMD centres. However, whilst facilitating comparison between surgical procedures and diagnostic groups, it must be acknowledged that

this would present a considerable challenge to investigators. Such practice would necessitate the standardisation of diagnostic and outcome criteria, psychometric assessment measures, length of follow-up period, patient selection criteria, surgical technique, and quality of post-operative rehabilitation (Feldman et al, 2001; Hay et al, 1993). Careful consideration of these issues may however result in a considerably more powerful research design, which is currently lacking within the evidence base.

The nature of future research within the field of chronic and refractory mental disorder may no longer be restricted to the evaluation of ablative neurosurgery. Although in their infancy, two additional interventions have emerged as potential alternatives to NMD, with the added advantage of being considered 'reversible'. Initial evidence has investigated the short and long term efficacy of deep brain stimulation in reducing core symptoms in treatment refractory OCD, with recent research providing evidence in support of the maintenance of symptom reduction in 4 patients, 21 months after surgery (Nuttin, Cosyns, Demeulemeester, Gybels & Meyerson, 1999; Nuttin, Gabriels, Cosyns, Meyerson, Andreewitch, Sunaert et al, 2003). The application of deep brain stimulation in the former research involved the bilateral placement of electrical stimulation electrodes in the anterior limbs of the internal capsules, the same area which is targeted in anterior capsulotomy.

Initial investigation has also begun regarding the application of vagus nerve stimulation in the treatment of intractable mental disorder. Currently an effective intervention in cases of refractory epilepsy, this procedure involves the electrical stimulation of fibres within the vagus nerve. Early reports from the United States

have suggested response rates of between 30 per cent and 37 per cent on primary outcome measures, following a ten week period of stimulation in patients with chronic depressive disorder (Sackeim, Rush, George, Marangell, Husain, Nahas et al, 2001). Vagus nerve stimulation was implemented at the Scottish centre as an intervention in cases of chronic depression for the first time in the UK, in 2001. This technique continues to be under evaluation, and is subject to the same pre- and post-operative neuropsychological assessment as that conducted with NMD patients. The possibility therefore exists that such alternative treatments could be considered as future control groups in neuropsychological and clinical outcome studies.

In summary, given the number of potentially contributing factors to the outcome observed following neurosurgery for mental disorder, it would appear critical that neuropsychological, psychiatric, surgical, and environmental factors are not considered in isolation in the design of any future research involving this particular population group.

4.11 Conclusion

Recent advances in our understanding of the neuropsychological and neurobiological underpinnings of the disorders for which NMD is indicated, alongside the future implementation of rigorously conducted outcome research, have the potential to develop a stronger theoretical and empirical basis on which the efficacy of such neurosurgical procedures can be evaluated. As such, in the presence of current safeguards and comprehensive evaluation, neurosurgery for mental disorder continues to occupy a valid place amongst a range of interventions for the small number of individuals to whom it may apply.

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APPENDIX

Ethical Approval Form & Confidentiality Statement

Tayside Committee on Medical Research Ethics

Level 9
Ninewells Hospital & Medical School
Dundee
DD1 9SY
Tel: 01382 632701/425598
Fax: 01382 496207
Email:

23 December, 2002

Response Form for Applicants

Reference Number: 248/02

Title of Proposal: Neuropsychological outcome of neurosurgery for mental disorders

First Researcher: Ms A A Livingstone, Trainee Clinical Psychologist, Department of Clinical Psychology, Ninewells Hospital & Medical School

Documentation Reviewed:

Proposal Form

This application has been considered and the Tayside Committee on Medical Research Ethics would like to make the following comments:

Since a new database is being established, you should consult the Data Protection Officer and the Caldicott Guardian, Dr Mutch.

APPROVAL IS GIVEN SUBJECT TO THE CONDITIONS SET OUT BELOW & ON THE FOLLOWING PAGE

Date of Review: 20 December 2002

List of Members in attendance: Mr A MacConnachie; Mr P K Brown; Dr J Davidson; Mr A S Jain; Dr W Stevenson; Dr M A R Thomson; Dr L Treliving

Conditions of Approval

- The Data Protection Officer and the Caldicott Guardian should be consulted about, and approve, the establishment of the new database.
- You should follow the protocol agreed and advise the Committee of any proposed amendments – no significant changes to the protocol should be made without the Ethics Committee/Chairman's approval.
- You must promptly inform the Ethics Committee of deviations from or changes to the protocol which are made to eliminate immediate hazards to the research subject; of any changes that increase the risk to subjects and/or affect significantly the conduct of the research; all adverse events that are both serious and unexpected; new information that

may adversely affect the safety of the subjects or the conduct of the research; if the research is abandoned for any reason.

- Each research proposal will be subject to a follow-up review and may be selected for a monitoring visit on behalf of the Tayside Trusts.
- You must start the project within three years of the date approval is given or the approval expires; extensions can be applied for; you are required to notify the Committee of the termination of the study.

It would be helpful if in the event of there being any future correspondence about this study, you could quote Ref: 248/02.

Signed

LREC ADMINISTRATOR

On behalf of the Tayside Committee on Medical Research Ethics

Alison Livingstone
Clinical Psychology Department
Level 6
Sth Block
Ninewells Hospital

Date 03 April 2003
Your Ref PMcK/FK/april01
Our Ref

Enquiries to Peter McKenzie
Extension 27920
Direct Line (01382) 527920
Email

Dear Ms Livingstone

NEUROPSYCHOLOGICAL OUTCOME OF NEUROSURGERY FOR MENTAL DISORDERS

Please find enclosed a copy of the authorised Confidentiality Statement submitted for this study.

Thank you for providing the information requested in our previous correspondence.

Yours sincerely

TAYSIDE PRIMARY CARE

CONFIDENTIALITY STATEMENT - for users of NHS person identifiable data



User Details

Name: ALISON LIVINGSTONE
Position: TRAINEE CLINICAL PSYCHOLOGIST
Organisation: DEPT. CLINICAL PSYCHOLOGY
Address: LEVEL 6, SOUTH BLOCK
NINEWELLS HOSPITAL
DUNDEE
Tel: 01382 425612

Sponsor Details

Name: PROFESSOR KEITH MATTHEWS
Position: PROFESSOR / Hon Lecturer
Psychiatry
Organisation: Univ. of Dundee
Address: DEPT OF PSYCHIATRY
NINEWELLS HOSPITAL, DUNDEE
Tel: 01382 632121

Data Protection Reg. No. :- ENCLOSED ; LETTER OF RESPONSE FROM DATA PROTECTION OFFICER

Data Requested :- BASIC DEMOGRAPHIC DETAILS OF PATIENTS INVOLVED IN SURGICAL PROCEDURE
- RAW SCORES FROM RANGE OF NEUROPSYCHOLOGICAL ASSESSMENTS HELD
WITHIN PATIENT'S PSYCHOLOGY AND PSYCHIATRY CASE NOTES.

Access required to health care records Yes No

Co-Users of the Data :- DR JUNE M. E. GILCHRIST
(CONSULTANT CLINICAL NEUROPSYCHOLOGIST)
- PROFESSOR KEITH MATTHEWS
(CONSULTANT PSYCHIATRIST)

Intended use of data (inc. publications) :

- CLINICAL AUDIT OF PREVIOUSLY COLLECTED ROUTINE CLINICAL DATA .
- POST-GRADUATE THESIS
- PUBLICATIONS